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# Fonction vasculaire dans les insuffisances circulatoires aiguës : du tonus vasomoteur au couplage ventriculo-artériel

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**Thèse de Doctorat**

*Mention Biologie Santé  
Spécialité Cardiologie-hémodynamique*

présentée à *l'Ecole Doctorale en Sciences Technologie et Santé (ED585)*

**De l'Université Picardie Jules Verne**

Par

**Guinot Pierre-Grégoire**

pour obtenir le grade de Docteur de l'université de Picardie Jules Verne

***Fonction vasculaire dans les insuffisances circulatoires  
aigues : du tonus vasomoteur au couplage ventriculo-  
artériel***

Soutenue le 23 Novembre 2017, après avis des rapporteurs, devant le jury d'examen :

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**M. Marc-Olivier Fischer, Professeur**

**M. Jean-Louis Gérard, Professeur**

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## Résumé

En anesthésie-réanimation, l'insuffisance circulatoire aigüe vasoplégique est une situation quotidiennement rencontrée (sepsis, chirurgie, polytraumatisme) qui implique une prise en charge rapide par l'utilisation d'un agent vasopresseur (noradrénaline, le plus souvent). Ce syndrome fait partie d'une atteinte plus large de la fonction vasculaire qui comprend une dysfonction de l'endothélium vasculaire et de ses fonctions de modulation du tonus vasculaire, de la perméabilité vasculaire, de la cascade de la coagulation et des cellules immunitaires.

Dans la première étude, nous avons démontré que la survenue d'un syndrome vasoplégique est associée à un trouble de la vasomotricité endothéliale dépendante de la voie du monoxyde d'azote (NO). Dans le deuxième travail, nous avons évalué le couplage ventriculo-artériel chez des patients avec une insuffisance circulatoire dite vasoplégique. L'analyse hémodynamique par une approche du couplage ventriculo-artériel (couplage V-A) caractérise mieux l'état hémodynamique qu'une approche conventionnelle (débit, résistances). L'indice de couplage ventriculo-artériel prédit l'évolution de la pression artérielle et du débit cardiaque avec un traitement par noradrénaline, contrairement aux variables hémodynamiques habituelles. Dans la troisième étude, nous avons décrit un nouvel indice hémodynamique permettant d'évaluer en temps réel le tonus vasomoteur (l'élastance artérielle dynamique), donc du besoin en noradrénaline. L'élastance artérielle dynamique prédit la dépendance de la pression artérielle à la noradrénaline. Dans le dernier travail, nous avons validé l'utilisation de cet indice au lit du malade pour optimiser le traitement par noradrénaline. Ces études soulignent l'impact clinique positif d'une nouvelle approche du syndrome vasoplégique en repositionnant notre « regard de l'hémodynamique » selon une approche dynamique : élastance artérielle dynamique et couplage ventriculo-artériel.

## **Liste des abréviations**

$C_A$  : Compliance artérielle

$D_c$  : Débit cardiaque

$F_c$  : Fréquence cardiaque

$E_{\text{dyn}}$  : Elastance artérielle dynamique

$E_A$  : Elastance artérielle

$E_V$  : Elastance ventriculaire

$F_{\text{eVG}}$  : Fraction d'éjection ventriculaire gauche

ICA : Insuffisance circulatoire aigüe

NO : Monoxyde d'azote

PAD : Pression artérielle diastolique

PAM : Pression artérielle moyenne

PAS : Pression artérielle systolique

POD : Pression de l'oreillette droite

PVC : Pression veineuse centrale

Pes : Pression télé-systolique ventriculaire gauche

RV : Retour veineux

RVS : Résistances vasculaires périphériques

VES : Volume d'éjection systolique

$V_{\text{eD}}$  : Volume télé-diastolique ventriculaire gauche

$V_{\text{eS}}$  : Volume télé-systolique ventriculaire gauche

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## 1. Introduction

### a. Une vision simplifiée du système cardio-vasculaire

Le système cardiovasculaire est composé du cœur, des vaisseaux sanguins et du sang (1). Le cœur et le système vasculaire sont anatomiquement et fonctionnellement connectés, bien qu'ils soient fréquemment étudiés séparément. L'arbre artériel n'agit pas uniquement comme un simple conduit de distribution du flux sanguin aux organes mais module aussi l'éjection ventriculaire, transformant une pulsatilité (volume) en un flux continu (pression) tout en maintenant une pression diastolique suffisante pour assurer la perfusion d'organes (1). Aussi la compréhension du fonctionnement du système cardio-vasculaire passe par la connaissance de la fonction cardiaque, de la fonction vasculaire et de l'interaction permanente de ces deux fonctions.

### i. La fonction cardiaque

Le cœur est un organe complexe dont la principale fonction est de transmettre de l'énergie au sang afin de générer et de maintenir une pression artérielle suffisante pour perfuser les organes (1). Le cœur répond à cette contrainte en contractant périodiquement ses parois musculaires autour d'une chambre afin de générer une pression suffisante pour propulser le sang du ventricule gauche dans l'aorte. Simultanément, le ventricule droit se contracte et propulse le sang dans l'artère pulmonaire pour perfuser les poumons, lieu d'échange en dioxyde de carbone et en oxygène (1).

Chaque fois que le cœur bat, un volume de sang (volume d'éjection systolique (VES)) est éjecté respectivement dans l'aorte et l'artère pulmonaire. Au final, le cœur génère un débit cardiaque ( $D_c$ ) qui est le produit du VES et de la fréquence cardiaque. Ce  $D_c$  répond aux besoins métaboliques de l'organisme. Le rôle du cœur peut être considéré de différentes manières: le cœur droit qui assure un retour veineux et les échanges pulmonaires, le cœur gauche qui distribue un débit sanguin. Les circulations pulmonaire (cœur droit) et systémique (cœur gauche) sont organisées en série de telle manière que toute augmentation du  $D_c$  est associée dans la même proportion à une augmentation du retour veineux. En revanche, les organes sont disposés de manière parallèle. Par conséquent, la majorité des organes reçoivent une quantité de sang avec une composition identique, et le débit sanguin est contrôlé

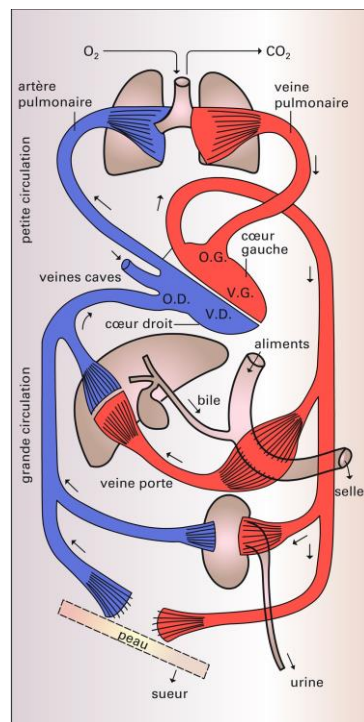


au travers de chaque organe indépendamment pour répondre à des besoins métaboliques spécifiques (2).

Plusieurs mécanismes interviennent dans la régulation du Dc : une régulation intrinsèque (mécanisme de Franck-Starling), un contrôle de la fréquence cardiaque et de l'inotropisme cardiaque par le système nerveux autonome, le baroréflexe, un contrôle des débits sanguins par des médiateurs neuro hormonaux, des médiateurs locaux, l'acidose, l'hypoxémie...(1, 3, 4)

## ii. Le système vasculaire circulatoire

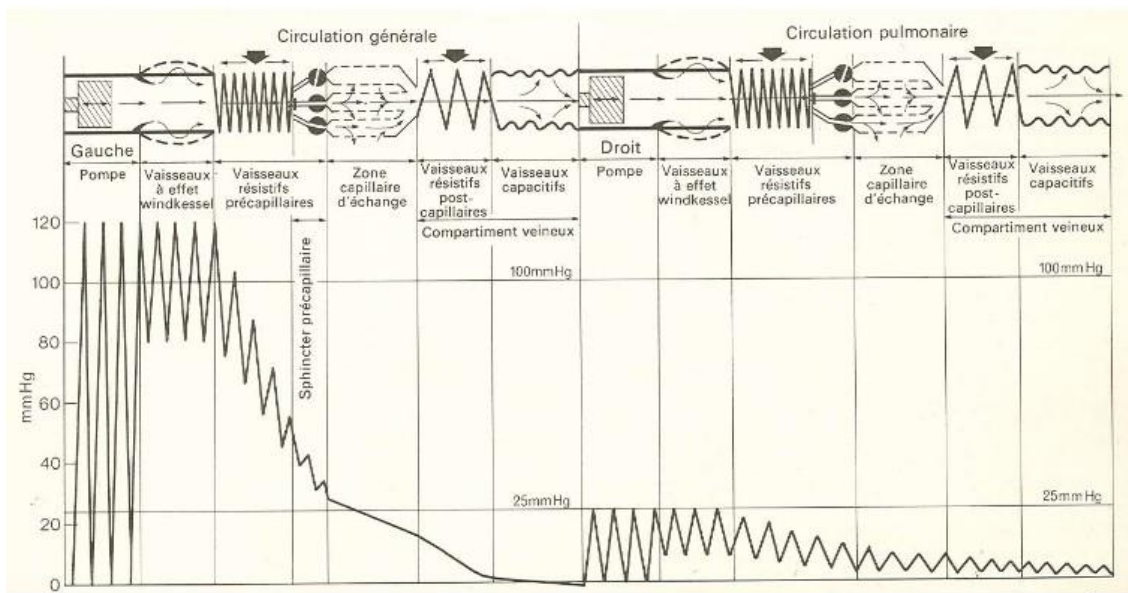
Le système circulatoire est constitué des vaisseaux sanguins (artères, capillaires, veines) qui amènent le sang aux tissus (artères), lieu d'échange (capillaires), puis le ramènent au cœur droit (veines) (Figure 1) (5, 6).



**Figure 1** : Représentation schématique du système vasculaire circulatoire.

La taille des vaisseaux sanguins diminue depuis le cœur jusqu'aux tissus. Deux types de vaisseaux sont décrits : les vaisseaux conductifs de gros calibre et les vaisseaux résistifs de petit calibre (5, 6). Les artères se divisent pour former des artérioles puis des capillaires qui sont le lieu d'échange entre le sang et les tissus. Sur le plan hémodynamique, le système vasculaire est séparé en un secteur dit à haute pression

(12% de la volémie) qui s'étend du ventricule gauche en systole jusqu'aux artérioles, et un secteur dit à basse pression (80% de la volémie) qui comprend les veines, le cœur droit, la circulation pulmonaire, l'oreillette gauche et le ventricule gauche en diastole. Entre ces deux secteurs, se situent les capillaires qui contiennent moins de 10% de la volémie. Ces secteurs diffèrent par leurs caractéristiques, fonctions et régime de pression (Figure 2) (5).



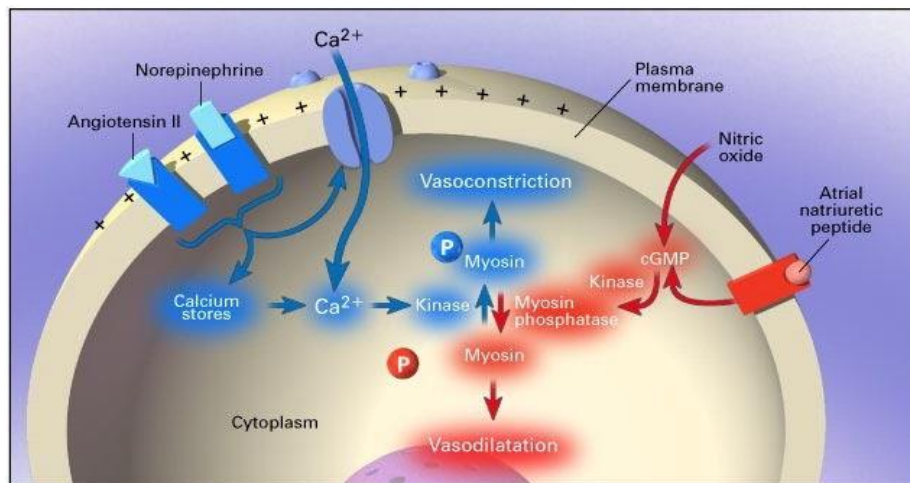
**Figure 2 :** Représentation schématique de la circulation avec les caractéristiques des différents segments.

L'une des principales fonctions du système vasculaire est d'assurer la distribution du débit sanguin aux différents organes par le maintien d'une pression de perfusion tissulaire. La pression artérielle ne peut être dissociée du débit sanguin car elle résulte de l'interaction entre le sang éjecté du ventricule gauche à chaque systole et le système vasculaire. En physiologie humaine, la pression artérielle motrice est la pression artérielle moyenne (PAM) qui est constante sur tout l'arbre vasculaire (7). Au niveau local, la répartition des débits sanguins est régulée en fonction de la demande de chaque tissu. Elle dépend de plusieurs mécanismes dont la mise en jeu plus ou moins rapide (baroréflexe, réflexe ischémique central, chémorécepteurs, système rénine-angiotensine, aldostérone) modifie la fréquence cardiaque, la contractilité myocardique, le volume sanguin, la viscosité sanguine et le tonus vasculaire (5-7). En situation physiologique, le flux sanguin régional (pression de

perfusion et débit sanguin régional) dépend principalement du tonus artériolaire déterminé par l'état contractile des cellules musculaires lisses de la paroi des vaisseaux. Grâce à la mise en jeu de ces mécanismes d'adaptation, le débit sanguin local d'un organe reste constant entre deux niveaux de pression artérielle (autorégulation). En dehors de ces limites, le débit sanguin local devient dépendant de la pression artérielle (phase de dépendance). Ainsi, le débit sanguin chute (augmente) si la pression de perfusion artérielle chute (augmente).

*Contrôle du tonus vasomoteur au niveau de la cellule musculaire lisse vasculaire*

Le contrôle du tonus vasomoteur dépend d'un équilibre entre des voies vasoconstrictrices et vasodilatatrices, l'état du potentiel de repos de la membrane de la cellule musculaire lisse et la mise en jeu de substances vasoconstrictrices/vasodilatatrices (Figure 3) (8).



**Figure 3** : Schéma représentant les différentes voies de régulation du tonus vasomoteur. Au repos, il existe un équilibre entre les voies vasoconstrictrices (bleues) et vasodilatatrices (rouges) (8).

- Voie vasoconstrictrice : la fixation d'un effecteur vasoconstricteur (noradrénaline, angiotensine) sur son récepteur membranaire augmente la concentration cytoplasmique de calcium (ouverture de canaux membranaires  $Ca^{2+}$  voltage dépendant et phénomène de libération à partir de

réerves cytoplasmiques) par l'intermédiaire d'un second messenger. Le  $\text{Ca}^{2+}$  forme un complexe avec la calmoduline qui active une kinase qui phosphoryle la myosine et active la myosine ATPase, entraînant la contraction musculaire (9).

- Voie vasodilatatrice : les substances vasodilatrices (FAN, monoxyde d'azote) activent une kinase qui interagit avec la myosine phosphatase qui déphosphoryle la myosine, empêchant toute contraction musculaire (10-12).
- En plus de ces phénomènes, il existe une régulation du tonus vasomoteur par l'état du potentiel de membrane de la cellule musculaire vasculaire. Une dépolarisation membranaire induit une entrée cytoplasmique de  $\text{Ca}^{2+}$  et active la cascade vasoconstrictrice. Une hyperpolarisation ferme les canaux  $\text{Ca}^{2+}$  et diminue la concentration cytoplasmique de  $\text{Ca}^{2+}$ , entraînant une relaxation musculaire. Le potentiel de membrane des cellules musculaires vasculaires dépend de nombreux canaux ioniques (9). Parmi ceux-ci, les canaux potassiques ATP dépendant ( $\text{K}_{\text{ATP}}$ ) ont un rôle prépondérant dans la genèse du choc vasoplégique (13). L'ouverture de ces canaux entraîne une sortie massive de  $\text{K}^+$  intracellulaire et empêche l'entrée de  $\text{Ca}^{2+}$  dans le cytoplasme. A l'état de base, ces canaux sont majoritairement fermés. Cette voie fut impliquée dans la résistance des vaisseaux à l'angiotensine et aux amines vasopressives (14). Les canaux  $\text{K}_{\text{ATP}}$  sont activés par la diminution de la concentration cellulaire d'ATP et une augmentation des concentrations cellulaires de  $\text{H}^+$  et de lactates (15). De même, certaines substances retrouvées dans le sepsis et le choc hémorragique peuvent directement activer ces canaux : atrial natriuretic peptide, calcitonin gene-related peptide, adénosine (16). Ainsi, toutes les situation physiopathologiques responsables d'une hypoxie tissulaire (sepsis, chirurgie cardiaque), d'une d'anaérobiose, d'une acidose lactique activent les canaux  $\text{K}_{\text{ATP}}$  des vaisseaux contribuant à une vasoplégie.
- Le NO produit par les cellules endothéliales et cellules musculaires lisses vasculaires (17, 18). De nombreux travaux réalisés dans le choc septique, le

choc hémorragique et en chirurgie cardiaque ont démontré une action vasodilatatrice du NO avec disparition de la vasoplégie lors de l'inhibition de la synthèse du NO (17-22). Le NO active une myosine phosphatase empêchant toute contraction musculaire. De même, il active des canaux potassiques  $Ca^{2+}$  sensibles ( $K_{ca}$ ) soit directement (*nitrosylation* du canal) soit indirectement (voie  $GMP_c$  dépendante), ce qui entraîne une hyperpolarisation membranaire, donc une vasoplégie (22).

- La vasopressine est la dernière voie impliquée dans la régulation du tonus vasomoteur (8). La vasopressine (hormone antidiurétique) est un peptide synthétisé dans l'hypothalamus qui exerce plusieurs fonctions : action antidiurétique (récepteurs V2 rénaux couplés à un signal AMPc dépendant), vasopressive (récepteurs V1 vasculaires couplés à un signal calcique), plaquettaire (récepteurs V2 plaquettaires), hormone hypophysiotrope en stimulant la sécrétion d'ACTH (récepteurs V3). L'effet vasomoteur de l'administration de vasopressine dépend de l'état du système nerveux végétatif et du système rénine-angiotensine (23, 24). Chez un sujet sain, l'effet vasoconstricteur de l'AVP est compensé par une bradycardie liée à l'activation du baroréflexe. Dans le cadre du syndrome vasoplégique associé à un sepsis ou un choc hémorragique, la vasoplégie fut associée à un défaut relatif d'AVP, une déplétion hypophysaire responsable d'une diminution des taux sanguins (24-26). Dans ces situations, l'administration d'AVP restaure un tonus vasomoteur et un niveau de pression artérielle.

### **iii. L'interaction cardio-circulatoire au travers de la charge artérielle**

La charge artérielle est décrite comme l'opposition à l'éjection ventriculaire gauche durant la systole (27). Elle peut être assimilée à un élément de post-charge cardiaque (28). La pression artérielle résulte de l'interaction entre le flux sanguin éjecté à chaque systole du ventricule gauche et la charge artérielle (27, 29). Ainsi, la charge artérielle est modulée pour maintenir une pression de perfusion constante. Autrement dit, la pression artérielle ne dépend pas que du Dc mais aussi de la charge artérielle.

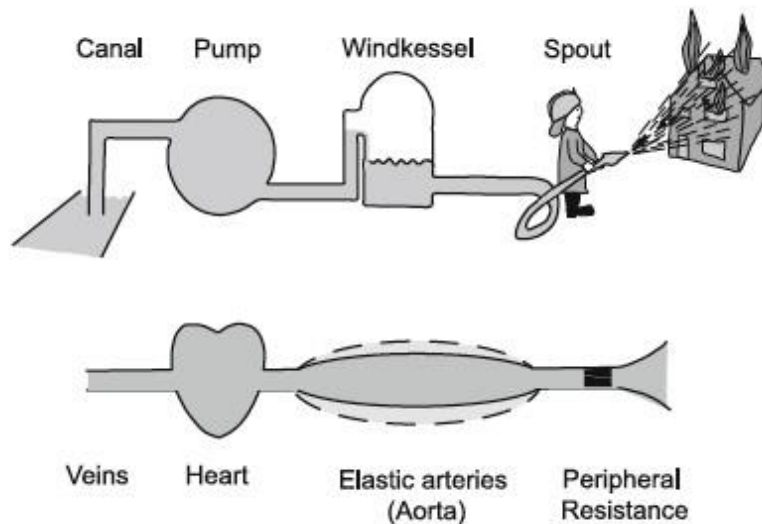
Dans l'approche classique (loi d'Ohm), la charge artérielle est approchée par les résistances vasculaires périphériques (RVS) qui sont calculées à partir du Dc, de la pression de l'oreillette droite (POD) et de la PAM selon la formule suivante (31):

$$RVS = (PAM - POD) / Dc.$$

Les RVS sont un paramètre calculé et non mesuré qui prend en compte le tonus vasomoteur, la viscosité sanguine et le débit sanguin (31). Cependant le système vasculaire n'est pas seulement résistif mais aussi capacitif puisqu'il restitue en diastole une partie du sang accumulé lors de la systole ventriculaire (31). La distribution des résistances vasculaires périphériques n'est pas homogène le long de l'arbre vasculaire (32). De plus, il existe au niveau tissulaire un phénomène de chute d'eau ou «waterfall» responsable du maintien de la perfusion tissulaire qui, s'il n'est pas pris en compte, peut surestimer ces résistances (33).

En raison de la nature oscillatoire de la pression artérielle et de l'écoulement continu du sang, le « gold standard » pour évaluer la charge artérielle est la mesure de l'impédance aortique (Z) (31, 34). L'impédance Z est le reflet de l'interaction complexe entre une pression pulsatile et le débit sanguin qui intègre les propriétés mécaniques du système artériel et les effets de réflexion des ondes artérielles (31). Cependant, en pratique clinique, la mesure de l'impédance est difficile et peu réalisable.

Le modèle de Windkessel permet de décrire la transformation d'un débit continu pulsé de sang en un débit continu (35). Initialement ce modèle fut décrit avec deux composants : les résistances vasculaires périphériques (composante continue résistive), et la compliance vasculaire (composante pulsatile) (Figure 4). Par la suite sa précision fut améliorée en ajoutant l'impédance aortique (modèle à 3 composants) puis l'onde de réflexion vasculaire (modèle à 4 composants).



**Figure 4:** Représentation schématique du modèle de Windkessel à 2 composants (35)

*L'élastance artérielle dynamique, un nouvel indice de charge artérielle*

Quelques auteurs, dont notre équipe, ont étudié une approche dynamique du tonus vasculaire basée sur la mesure de l'élastance artérielle dynamique ( $E_{a_{dyn}}$ ) (36, 37).  $E_{a_{dyn}}$  représente le rapport entre la variation respiratoire de la pression pulsée et la variation respiratoire du volume d'éjection systolique (38). Ce paramètre dynamique informe battement par battement d'une élastance artérielle dont le reflet physiologique exact n'est pas connu. Hadian et al ont démontré que cet indice diminue avec l'administration d'un vasodilatateur pur et qu'il augmente avec un vasoconstricteur (38). Une étude récente proposerait l' $E_{a_{dyn}}$  comme un indice de couplage ventriculo-artériel (39). L'auteur de ce travail de thèse pense que l' $E_{a_{dyn}}$  serait plutôt un reflet du tonus capillaire et du couplage entre le système macrovasculaire et microvasculaire. Un avantage est que l' $E_{a_{dyn}}$  est calculée en temps réel et continu lors du monitoring hémodynamique des patients.

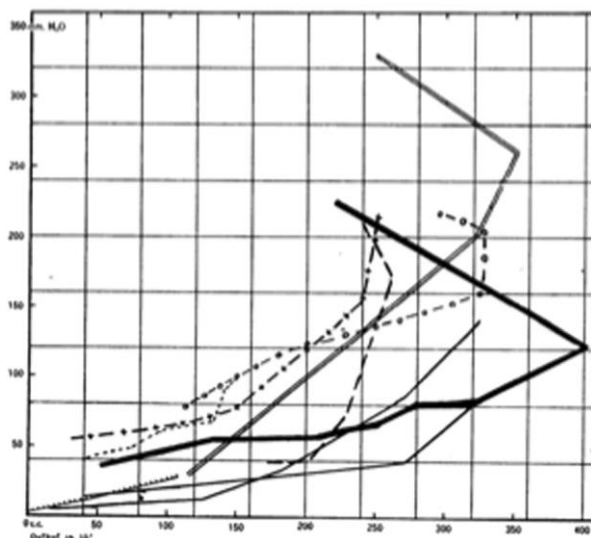
**b. Description hémodynamique du système cardio-vasculaire**

L'hémodynamique est l'étude des lois régissant le fonctionnement du système cardio-vasculaire (40). Dans le cadre d'une approche dite « classique », le système vasculaire et la fonction ventriculaire gauche sont étudiés séparément. La performance cardio-vasculaire étant le résultat d'une interaction continue entre le cœur et le système vasculaire, chaque composant doit être évalué (le ventricule et le réseau vasculaire). Partant de ce principe, deux concepts différents permettent de

décrire le système cardio-vasculaire. Le premier est basé sur la combinaison des courbes de Franck-Starling et de retour veineux de Guyton, le deuxième décrit une interaction entre deux chambres élastiques, le système vasculaire et le ventricule gauche.

### i. Le concept de Franck-Starling

À la fin du 19ème siècle, Otto Frank a trouvé en utilisant des cœurs de grenouille isolés que la force de la contraction ventriculaire était augmentée lorsque le ventricule était étiré avant la contraction (41). Cette observation a été étendue par les études d'Ernest Starling qui ont démontré en 1914 que l'augmentation du retour veineux au cœur augmentait la pression télé-diastolique du ventricule gauche, et entraînait une augmentation du VES (42-44). À l'inverse, la diminution du retour veineux diminuait le VES (Figure 5). Cette réponse aux modifications du retour veineux (et de la pression de remplissage ventriculaire) est un phénomène intrinsèque au cœur qui ne dépend pas de facteurs extrinsèques (neurohumoraux...) (44). En l'honneur de ces deux premiers pionniers, la capacité du cœur à changer sa force de contraction et donc le VES en réponse aux changements de retour veineux (précharge) s'appelle le mécanisme Frank-Starling (ou la loi de Starling du cœur) (43).



**Figure 5** : Résultats originaux de l'expérience de Franck Starling. La pression auriculaire droite est en ordonnée, et le débit cardiaque en abscisse (42)

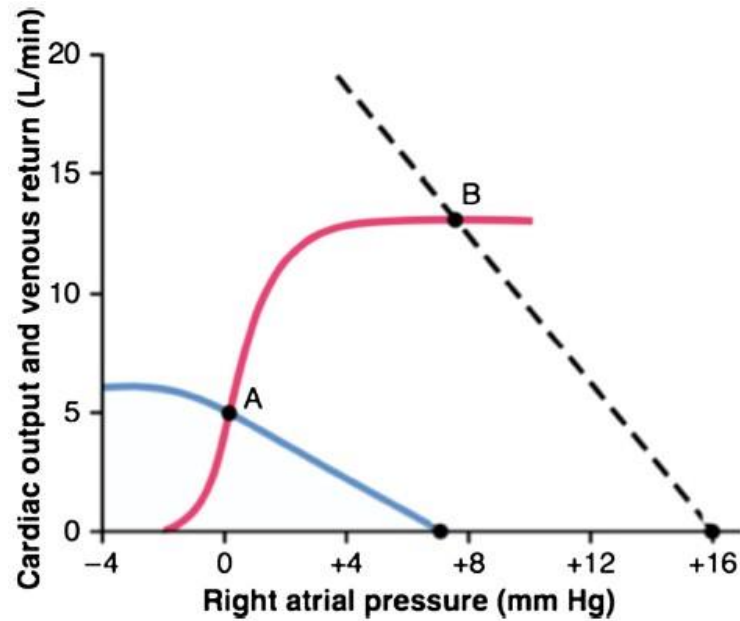


Par la suite, Sarnoff et Berglund ont confirmé les résultats de Franck et Starling, et la « loi du cœur » (45, 46). Ces auteurs ont par ailleurs démontré qu'il existe non pas une courbe mais en réalité une famille de courbes qui décrivent la relation entre la pression auriculaire droite, le travail cardiaque et le débit cardiaque (46). Chacune des courbes de Frank-Starling est définie par la post charge et l'inotropisme cardiaque (47).

## **ii. Le concept de Guyton**

Une compréhension plus complète de la relation entre la POD et la loi de Starling exige une connaissance du retour veineux. Au cours des années 1950 à 1970, Guyton a intégré ces fonctionnalités dans un modèle complet de la circulation et de contrôle du débit cardiaque (48-51). Guyton a confirmé que l'activité métabolique des organes périphériques est un facteur de régulation du retour veineux au cœur (donc du Dc) (51). Selon le modèle de Guyton, le retour veineux dépend du gradient de pression entre la pression systémique moyenne et la POD. Une POD élevée s'oppose au retour veineux. Par conséquent, le gradient entre la pression systémique moyenne et la POD conditionne le retour veineux, donc le Dc.

Guyton a combiné les courbes de Franck-Starling et celles du retour veineux (49). L'intersection de ces deux courbes détermine le DC pour une situation donnée. Selon cette courbe, la quantité de sang qui retourne au cœur (retour veineux) dépend de la pression systémique moyenne, de la POD, et de la résistance au retour veineux (Figure 6, point A) (49). La courbe de la fonction cardiaque sinusoïdale dépend de la surcharge post-ventriculaire, du tonus vasomoteur et de nombreux facteurs intrinsèques qui déterminent la performance cardiaque. Une augmentation du retour veineux déplace la courbe vers le haut (Figure 6, point B), le Dc augmentant dans une certaine limite (49).

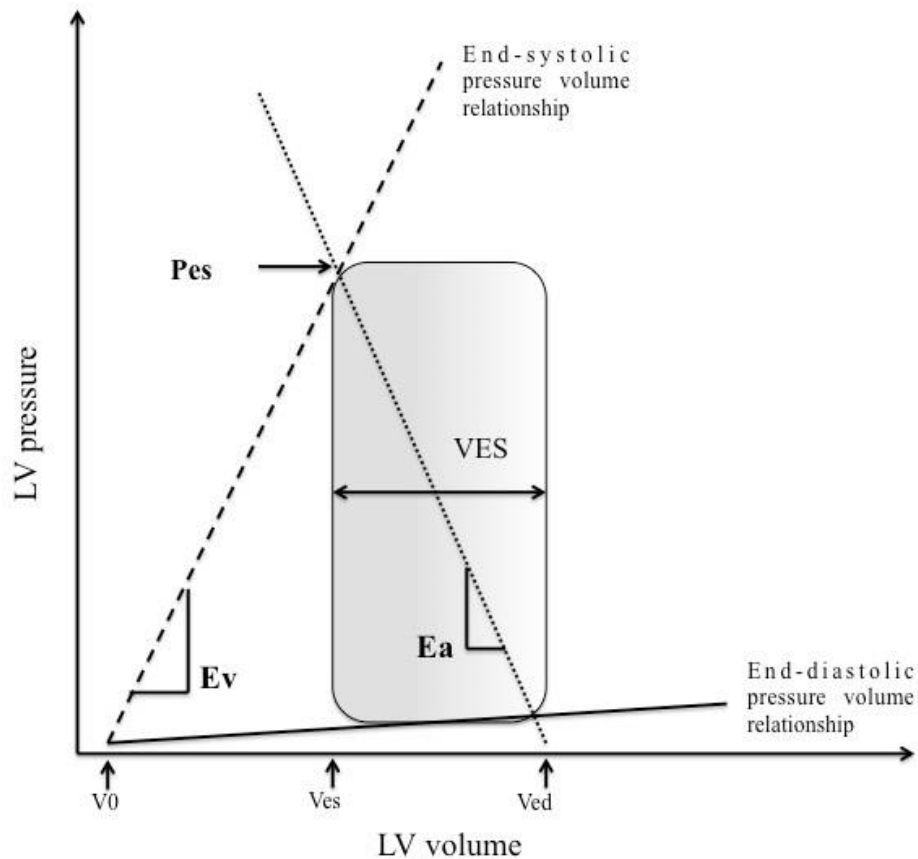


**Figure 6 :** Combinaison des courbes de Franck-Starling et de retour veineux pour modéliser la circulation (51)

### iii. Le concept du couplage ventriculo-artériel

Suga et Suganawa ont développé une approche complémentaire à celle de Guyton et Franck-starling, où le  $D_c$  est conditionné par le cœur et dépend de ses capacités contractiles (inotropisme), de sa précharge et de sa postcharge (27, 52-54). La pression artérielle dépend de la qualité du système artériel (compliance, résistances vasculaires) et de la quantité de sang éjecté par le cœur. C'est l'interaction permanente de ces deux chambres élastiques pendant un cycle cardiaque (systole, diastole) qui conditionne l'efficacité du système cardiovasculaire (Figure 7) (55).

L'élastance définit une variation de pression en rapport avec une variation de volume. Elle caractérise la relation entre le VES et la pression d'éjection ( $P_{es}$ ). Sunagawa et al ont développé un modèle s'intéressant à la relation pression-volume du ventricule gauche et du système vasculaire (27, 54, 56) (Figure 7). Cette approche se base sur la mesure de l'élastance ventriculaire gauche télé-systolique ( $E_V$ ) et de l'élastance artérielle ( $E_A$ ). Suite à l'éjection ventriculaire gauche, le système cardiovasculaire assure un débit et une perfusion tissulaire adéquate grâce à une adaptation permanente de l'élastance du système artériel avec l'élastance ventriculaire gauche.



**Figure 7:** Courbe pression-volume ventriculaire gauche. L' $E_V$  (élastance ventriculaire) est déterminée par la pente de la relation entre la pression télé-systolique (PTS) et le volume télé-systolique ventriculaire gauche à différents niveaux de charge. L' $E_A$  (élastance artérielle) est déterminée par la pente négative de la ligne reliant le volume télé-diastolique ( $V_{ed}$ ) et le point  $P_{es}$ .  $VES$  : Volume d'éjection systolique,  $V_{es}$  : Volume télé systolique  $V_0$  représente le volume ventriculaire résiduel.

### Élastance ventriculaire gauche ( $E_V$ )

L' $E_V$  représente la contractilité ventriculaire, qui est déterminée par la pente de la droite  $E_{max}$  sur la courbe pression volume (Figure 7). La droite  $E_{max}$  représente la relation entre la pression et le volume en fin de systole à différents niveaux de charge (57, 58). Celle-ci représente le meilleur moyen de caractériser l'ínotropisme (59).

$$E_v = [P_{(t)} / (V_{(t)} - V_0)]_{max}$$

$P_{(t)}$  et  $V_{(t)}$  sont les pressions et volumes ventriculaires gauches respectivement et  $V_0$  le volume mort.  $E_V$  est déterminée par la pente de la relation entre la pression de fin

de systole et le volume à différents niveaux de charge. L'équation de cette droite d'élastance ventriculaire est donnée par :

$$P_{es} = E_V (V_{es} - V_0) = E_V (V_{ed} - V - SV)$$

où  $P_{es}$  et  $V_{es}$  sont la pression et le volume de fin de systole,  $V_{ed}$  le volume de fin de diastole et  $SV$  le volume éjecté.  $V_0$  est l'intersection de cette droite avec l'axe des abscisses (Figure 7).

### *Élastance artérielle ( $E_A$ )*

En corollaire, par ses propriétés élastiques et résistives, le réseau vasculaire systémique représente une contrainte physique qui fixe les caractéristiques de l'environnement dans lequel la pompe doit opérer (Figure 7) (27). L'impédance d'entrée de l'aorte ascendante fournit la description la plus complète de la charge hydraulique à laquelle le ventricule gauche est confronté puisqu'elle caractérise complètement le réseau vasculaire (28, 60). En effet, cette impédance prend en compte plusieurs paramètres comme la compliance, les résistances périphériques, la résistance des gros vaisseaux. L'utilisation d'un modèle de Windkessel à 3 (ou 4) éléments permet de calculer séparément les différents composants de cette impédance (résistance des gros vaisseaux, résistance périphérique et compliance) afin d'exprimer cette impédance sous la forme d'une  $E_A$  (61). Sunagawa et al ont démontré que cette charge artérielle pouvait être caractérisée dans le domaine temporel par l' $E_A$  (54). L' $E_A$  est un indice qui intègre les principaux composants de cette charge artérielle, et peut être considérée comme une mesure de la charge artérielle nette imposée au VG (28). Les différents éléments du modèle de Windkessel peuvent être exprimés dans le domaine temporel sous forme d'une élastance par la relation suivante (62) :

$$E_A (WK) = RT / [ts + (1 - e^{-td/\tau})]$$

où  $RT$  est la résistance vasculaire totale, égale à la somme de la résistance caractéristique du système (gros vaisseaux) et de la résistance périphérique.  $\tau$  est la constante de temps de décroissance diastolique de l'onde de pression égale au

produit de RT et de la compliance de l'arbre vasculaire (C). ts et td sont respectivement les temps de systole et de diastole.

#### *Couplage ventriculo-artériel ( $E_A/E_V$ )*

L'étude du couplage ventriculo-artériel, défini comme le rapport de l' $E_A$  et de l' $E_V$ , permet l'évaluation de l'efficacité de ce transfert d'énergie du myocarde vers le système artériel, autrement dit la performance myocardique (index de couplage normal  $E_A/E_V = 1 \pm 0,36 \text{ mmHg.ml}^{-1}$ ) (53, 55, 63). Sur le plan théorique, un défaut de couplage peut être secondaire à une atteinte d'un ou deux déterminants du couplage ventriculo-artériel (baisse de l' $E_V$  (choc cardiogénique, postcharge élevée), baisse de l' $E_A$  (choc vasoplégique), baisse de l' $E_V$  et l' $E_A$  (choc septique avec dysfonction myocardique)). L'évaluation de la performance cardio-vasculaire requiert donc d'abord de caractériser chacun de ses constituants : le réseau vasculaire systémique et la contractilité ventriculaire gauche. Ces deux composants opèrent de manière simultanée de telle sorte que leur interaction, c'est-à-dire le couplage, détermine le VES et la pression d'éjection (donc la pression artérielle) (63).

A partir du concept de couplage ventriculo-artériel, le volume d'éjection systolique (débit cardiaque) est décrit par la relation suivante :

$$\text{VES} = [E_V (\text{Ved} - V_0)] / [E_V + E_A]$$

### **c. Insuffisance circulatoire**

#### **i. Définition**

L'insuffisance circulatoire aiguë (ICA) est définie par une incapacité du système circulatoire (pompe cardiaque et/ou système vasculaire) à répondre à la demande en oxygène ( $O_2$ ) de l'organisme. Sur le plan physiopathologique, l'ICA correspond donc à une insuffisance respiratoire cellulaire aiguë, c'est-à-dire à un déséquilibre entre les besoins en  $O_2$  et les apports cellulaires en  $O_2$  (64). En effet, l' $O_2$  est un élément essentiel du métabolisme aérobie des cellules. Si l' $O_2$  ne parvient plus aux cellules, celles-ci s'orientent vers un métabolisme anaérobie avec production de lactates et d'ions  $H^+$ , et diminution de la synthèse d'ATP (64, 65).

Indépendamment de sa cause, l'ICA se traduit le plus souvent par une baisse du débit cardiaque et/ou une vasodilatation artério-veineuse (hypotension artérielle). Des

phénomènes adaptatifs sont rapidement mis en jeu pour améliorer et/ou rétablir un équilibre entre les apports en O<sub>2</sub> et la consommation en O<sub>2</sub>. Ces mécanismes sont une augmentation de l'extraction périphérique tissulaire en oxygène et une redistribution des débits sanguins régionaux en faveur des circulations vitales (cerveau, cœur). Malgré la mise en place de ces mécanismes, des lésions tissulaires et cellulaires hypoxiques peuvent apparaître et aggraver secondairement cet équilibre.

Plusieurs tableaux d'insuffisance circulatoire aiguë sont décrits : cardiogénique, vasoplégique, obstructif... (64, 65). Dans le cadre de ce travail, seul le syndrome vasoplégique est traité.

## **ii. Le syndrome vasoplégique**

L'ICA vasoplégique correspond à un défaut de perfusion tissulaire en rapport avec une hypotension artérielle par vasodilatation périphérique et un défaut de réponse des cellules musculaires lisses aux substances vasoactives (8). Les principales étiologies d'un syndrome vasoplégique sont le sepsis, l'hypotension artérielle prolongée, le choc hémorragique, le choc cardiogénique, la circulation extracorporelle, l'arrêt cardio-respiratoire, le choc anaphylactique, l'insuffisance hépatique et les intoxications (nitrogène, metformine, monoxyde de carbone, cyanure) (8).

Le choc vasoplégique est associé à une augmentation des concentrations plasmatiques de catécholamine avec activation du système rénine-angiotensine (66-68). Plusieurs mécanismes ont été proposés pour expliquer cet état, y compris la mort des cellules musculaires lisses vasculaires, une insuffisance d'extraction en oxygène et une augmentation de l'activité des prostaglandines avec une activité vasodilatatrice (69-71).

En raison de son importance clinique, le choc septique est le plus étudié des chocs vasoplégiques. Même si des similitudes existent entre la pathogénie du syndrome vasoplégique en chirurgie cardiaque et le choc septique (réaction inflammatoire, activation des macrophages et libération de cytokines), la généralisation des résultats du choc septique doit être faite avec précaution, car il est probable que les mécanismes physiopathologiques diffèrent selon le type de choc vasoplégique. Par exemple, la vasodilatation associée à l'intoxication au monoxyde de carbone peut être partiellement médiée par l'hypoxie tissulaire mais aussi par l'activation de la guanylate cyclase (72). Néanmoins, il peut exister des mécanismes communs expliquant la résistance aux vasopresseurs observée dans la plupart des types de choc

vasoplégique. Par exemple, trois mécanismes sont impliqués dans ce syndrome quelle que soit l'étiologie : activation des canaux  $K_{ATP}$ , activation de la forme inductible du monoxyde d'azote et déficience de l'arginine-vasopressine (8).

Lors de la chirurgie cardiaque, plusieurs facteurs (antécédents médicaux et médicamenteux, traumatismes tissulaires, hypoxie tissulaire, phénomènes d'ischémie-reperfusion, cardioplégie, utilisation d'un circuit de circulation extra-corporelle) entraînent l'activation de la voie du complément, la libération de cytokines pro-inflammatoires, une augmentation du stress oxydatif, une augmentation du monoxyde d'azote par surexpression de la NO synthétase inductible, une augmentation du taux de thromboxane  $A_2$ , une augmentation de cyclo oxygénase (73-79). Ces réponses sont concomitantes et coexistent avec comme conséquences une inflammation non contrôlée et une immunodépression qui vont entraîner une dysfonction vasculaire avec atteinte de l'intégrité endothéliale et de la régulation du tonus vasomoteur (76, 8).

Le NO semble tenir un rôle pivot dans l'atteinte de la régulation du tonus vasomoteur (19, 20, 22, 79). Le NO est produit par des enzymes dites constitutives et inductibles dans une large variété de cellules (endothéliales, macrophages, cardiomyocytes...) (79, 80). Le NO intervient dans la régulation du tonus vasomoteur avec des effets vasodilatateurs (79). Plusieurs études en chirurgie cardiaque ont démontré une diminution de l'activité de la NO synthétase constitutive (20, 22, 81-83). De même, lors de l'ischémie-reperfusion, la production de radicaux libres au travers du stress oxydatif diminue la biodisponibilité du NO (82).

#### **d. Positionnement du travail de thèse**

Ce travail est centré sur une problématique de compréhension de la physiopathologie et de la prise en charge hémodynamique du syndrome vasoplégique en péri-opératoire de chirurgie cardiaque.

Un premier axe de recherche entreprend de prédire et anticiper la survenue du syndrome vasoplégique en péri-opératoire de chirurgie cardiaque par une recherche axée sur la physiopathologie du syndrome vasoplégique.

Un deuxième axe repositionne l'analyse hémodynamique du syndrome vasoplégique selon une approche basée sur l'étude du couplage ventriculo-artériel afin d'en prédire la réponse hémodynamique au traitement par noradrénaline.

Un troisième axe de recherche est centré sur la mesure de l'élastance artérielle dynamique, sa signification physiologique et son applicabilité dans le syndrome vasoplégique.



## 2. Etudes

### a. Le syndrome vasoplégique est associé à (et précédé par) une atteinte de la réponse vasomotrice endothéliale

Le syndrome vasoplégique est une atteinte fréquente après chirurgie cardiaque avec une incidence allant jusqu'à 40% des patients selon les études (75). D'un point de vue physiopathologique, ce syndrome est la résultante d'une interaction multifactorielle et complexe qui active diverses voies enzymatiques et stimule la production et la libération de médiateurs de l'inflammation. L'ensemble de ces mécanismes entraîne d'une part l'activation de plusieurs mécanismes vasodilatateurs (canaux  $K_{ATP}$ , NO, déficit en vasopressine) et d'autre part une résistance aux vasopresseurs (hyperpolarisation membranaire) (73-78). Au final, apparaît un syndrome vasoplégique.

A ce jour, en dehors de quelques facteurs de risques clinico-biologiques décrits, aucun score clinique, test clinique ou examen paraclinique ne permet de prédire la survenue de ce syndrome (73-78). En pratique clinique, la mesure du flux sanguin et du diamètre lors du test de vasodilatation de l'artère brachiale (FMD) est un outil facile à utiliser et non invasif pour évaluer la vasodilatation vasculaire dépendante de la production endothéliale NO (84). Ce test est très étudié en cardiologie où il est associé à la survenue d'événements cardiovasculaires (85). En chirurgie cardiaque, quelques travaux suggèrent une atteinte de la production de NO mais aucun n'a évalué l'association entre la FMD, son évolution et la morbidité post-opératoire (83). A partir des données sur la physiopathologie du syndrome vasoplégique et sur la signification de la mesure de la FMD, l'auteur de cette thèse et son groupe de travail ont émis l'hypothèse que le syndrome vasoplégique est associé à une atteinte de la FMD et du tonus vasomoteur, que cette atteinte précède l'expression clinique et en est prédictive.

Ainsi, une étude observationnelle incluant 28 patients programmés en chirurgie cardiaque avec circulation extracorporelle fut réalisée. La FMD était mesurée avant et immédiatement après chirurgie cardiaque selon les recommandations internationales (84). Les résultats de ce travail démontrent plusieurs points : (1) avant chirurgie, les patients ne diffèrent pas en terme de FMD, donc de réactivité vasculaire et de production de NO ; (2) la chirurgie est associée à une atteinte de la FMD qui diminue en raison de la diminution de la production de NO ; (3) les patients qui développent un syndrome vasoplégique ont une réponse anormale de la FMD

avant même l'apparition de ce syndrome clinique ; (4) la mesure du diamètre de l'artère brachiale et de la FMD est prédictive de la survenue d'un syndrome vasoplégique.

Ce travail démontre bien l'association entre la survenue d'un syndrome vasoplégique et l'atteinte du tonus vasomoteur liée à la production endothéliale de NO. Les changements de diamètre de l'artère brachiale et de la FMD sont dus à des altérations de la réponse vasomotrice liée au NO. La chirurgie cardiaque est démontrée pour être associée à une atteinte de la production de NO. Cette atteinte est liée à une diminution de l'activité de la NO synthétase constitutive et une augmentation de l'activité de la NO synthétase inductible (86-88). Aucune des études ayant évalué la production endothéliale de NO n'avait étudié l'impact clinique de ces modifications.

[Click here to view linked References](#)

1

1 **Postoperative vasoplegic syndrome is associated with an impaired endothelial**  
2 **vasomotor response in cardiac surgery: a prospective observational study.**  
3

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## ABSTRACT

**Background:** Vasoplegic syndrome (VS) affects up to 30% of cardiac surgery patients. The occurrence of VS may be linked to the administration of nitric oxide (NO). The brachial artery's response to NO can be assessed with flow-mediated vasodilatation (FMD). The present study's main objective was to assess the brachial artery's diameter and FMD response immediately after cardiac surgery.

**Methods:** We performed a prospective, observational study at a tertiary care centre in Amiens, France. The main inclusion criterion was elective cardiac surgery with cardiopulmonary bypass. The primary outcome measures were the brachial artery diameter and the FMD response in patients with and without VS.

**Results:** Of the 28 patients included, 11 (39%) developed VS. Brachial artery diameter and FMD differed when comparing VS and non-VS patients. On ICU admission, the mean  $\pm$  standard deviation brachial artery diameter was larger in VS patients than in non-VS patients (39 mm  $\pm$  7 and 30 mm  $\pm$  8, respectively;  $p=0.002$ ). Likewise, the FMD response after surgery was greater in VS patients than in non-VS patients (42%  $\pm$  8 vs. 31%  $\pm$  1; respectively;  $p=0.014$ ). The brachial artery diameter and the FMD response after surgery were both predictive of VS, with an area under the curve [95% confidence interval] of 0.850 [0.705–0.995] ( $p=0.002$ ) and 0.755 [0.56–0.95] ( $p=0.047$ ), respectively.

**Conclusion:** Patients who developed VS had a larger brachial artery diameter and FMD response after cardiac surgery. Cardiac surgery with cardiopulmonary bypass appears to alter the NO-mediated endothelial vasomotor response.

**Keywords:** vasoplegic syndrome, flow-mediated vasodilatation, cardiac surgery, norepinephrine, NO-mediated dilatation.

## Background

Cardiac surgical vasoplegic syndrome (VS) is a form of acute circulatory failure characterized by persistent arterial hypotension requiring vasopressor treatment (1; 2). 9% to 44% of patients following cardiac surgery with cardiopulmonary bypass present this syndrome (3) that leads to inadequate tissue perfusion and metabolic acidosis, and increases postoperative morbidity. From a physiopathological perspective, VS results from a multifactorial, complex interaction between plasma proteins, leukocytes, platelets, and endothelial cells (4). Surgical trauma and the use of cardiopulmonary bypass (with exposure of blood to non-biological surfaces) activate various enzyme pathways and stimulate the production and release systemic and neurohumoral inflammatory mediators (5).

At the bedside, flow-mediated dilatation (FMD) is an easy-to-use, non-invasive tool for assessing nitric oxide (NO)-mediated vascular vasodilatation. NO is a major factor associated with vasomotor regulation (6). It has been shown that the endothelium's release of NO is altered after cardiac surgery (7). Thus, cardiac surgery with cardiopulmonary bypass is associated with a decrease in brachial artery diameter and the FMD response. However, the possible associations between these changes and clinical outcomes (such as VS) have never been evaluated.

We hypothesised that endothelial NO vasodilation may be altered before the clinical occurrence of VS, and then tested this hypothesis by using FMD. The main objectives of the present study were to (i) measure the FMD response before and after cardiac surgery with cardiopulmonary bypass, and (ii) assess the response's ability to predict the occurrence of VS.

## Methods

### *Ethical approval*

The study protocol was approved by the local independent ethics committee (*Comité de Protection des Personnes Nord-Ouest II*, Amiens, France; reference 2015-A01621) on November 26<sup>th</sup>, 2015. The present report was drafted in line with the STROBE statement for cohort studies. The study complied with the Declaration of Helsinki on ethical principles for medical research involving human subjects. All patients provided written, informed consent prior to the surgery.

### *Patient population*

A prospective, observational study was performed in Amiens University Hospital's cardio-thoracic ICU over a six-month period in 2016. The main inclusion criteria were as follows: age over 18, cardiac surgery with the use of cardiopulmonary bypass (coronary artery bypass grafting (CABG), surgical correction of valvular disease, a combination of the two, or surgery on the ascending aorta). The main non-inclusion criteria were permanent arrhythmia (atrial fibrillation or frequent ectopic beats), redo surgery, pregnancy, legal guardianship or incarceration, a functional implanted cardiac pacemaker, hypothermia, refusal to participate, sepsis, and age under 18.

### *Intra-operative procedure*

Anaesthesia and cardiopulmonary bypass procedures were standardised for all patients (8). No premedication was performed. Anaesthesia was induced with propofol and sufentanil. Tracheal intubation was facilitated with atracurium. Anaesthesia was maintained by target-controlled infusions of propofol and sufentanil. Titration of hypnotics and opioids was based on the bispectral index (Covidien, Boulder, CO, USA), according to published algorithms. Cardiopulmonary bypass with a heart-lung machine (Stockert Sorin S5 Heart Lung, Milan, Italy) was performed at a target blood flow of 2.4 l min<sup>-1</sup>m<sup>-2</sup>. The mean arterial blood pressure (MAP) was maintained at more than 65 mmHg by increasing the pump flow rate or, if then required, by administering a bolus of phenylephrine or norepinephrine. During cardiopulmonary bypass, normothermia

(bladder temperature  $>36^{\circ}\text{C}$ ) was maintained with a venous perfusion temperature of  $37^{\circ}\text{C}$ . Homologous red blood cell transfusions were given to patients with a haemoglobin value below  $8\text{ g dl}^{-1}$ . Depending on the surgical procedure, myocardial protection was ensured with antegrade cardioplegia (via the aortic root or the coronary ostia) and/or retrograde cardioplegia (via the coronary sinus). None of the study participants underwent intraoperative hemofiltration. None of patients was treated with corticosteroids or serine protease inhibitors.

#### *Postoperative procedures*

At the end of the surgical procedure, all patients were sedated with propofol and mechanically ventilated until (i) haemodynamic stability and normothermia were achieved and (ii) the blood loss was considered acceptable (less than  $1\text{ ml kg}^{-1}\text{ h}^{-1}$ ). Patients were treated by physicians trained in postoperative cardiac surgical care (including a cardiologist). Circulatory support was guided by institutional protocols designed to achieve predefined endpoints: a MAP above  $65\text{ mmHg}$ , a cardiac index (CI) above  $2.2\text{ l min}^{-1}\text{m}^{-2}$ , and urine output above  $0.5\text{ ml kg}^{-1}\text{ h}^{-1}$  (9, 10).

#### *Haemodynamic parameters*

Transthoracic echocardiography (CX50 Ultrasound System and an S5-1 Sector Array Transducer, Philips Medical System, Suresnes, France) was performed by a physician blinded to the study results. The left ventricular ejection fraction (LVEF) was calculated using Simpson's method on a four-chamber view. The diameter of the left ventricular outflow tract was measured on a long-axis parasternal view at the time of patient inclusion. The aortic velocity-time integral (VTIAo), the pre-ejection time and the systolic time were measured with pulsed Doppler on a five-chamber apical view. Stroke volume (SV; mL) was calculated as  $\text{VTIAo} \times \text{aortic area}$ . The CI ( $\text{l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ ) was calculated as indexed stroke volume  $\times$  heart rate (HR). The systemic vascular resistance index (SVRi) was calculated as the  $\text{MAP} - \text{central venous pressure}/\text{CI}$  ( $\text{mmHg}\cdot\text{ml}^{-1}\cdot\text{m}^{-2}$ ).

### *Brachial artery diameter and the FMD response*

The FMD response was measured according to the international guideline on brachial artery reactivity (11). Brachial artery diameter was measured by ultrasound with an 8-10 MHz linear array probe (Phillips CX50, Philips Medical System, Suresnes, France). The artery diameter was measured before FMD testing. Next, a blood pressure cuff was inflated to at least 50 mmHg above the patient's systolic arterial pressure for five minutes, and was then released to induce hyperaemia. During the following two minutes, images were acquired continuously with high-resolution M mode ultrasound. All stored images were uploaded to a server, and the diameter was measured offline by using DICOM viewer software (Oxiris®, Pixmeo SARL, Bernex, Switzerland). The FMD response was calculated according to the following equation: [FMD response (%) = (maximum diameter – minimum diameter)/maximum diameter]. Before cardiac surgery, a cross was drawn on the arm with a marker pen so that the same site would be used for the post-surgery measurement. The same physician performed all FMD measurements.

### *Performance of the study*

Demographic, intraoperative and postoperative data were prospectively recorded on admission to the ICU and then after surgery. Vasoplegic syndrome was defined as persistent arterial hypotension (i.e. a MAP below 65 mmHg) despite fluid resuscitation, and the need for norepinephrine infusion to maintain or restore a MAP over 65 mmHg for more than 4 h (9, 10). VS was screened during the first 48 hours stay in ICU.

### *Statistics*

The distribution of variables was assessed using Kolmogorov-Smirnov test. Data were expressed as the mean ± standard deviation (SD), the median [interquartile range] or the number (percentage), as appropriate. The study population was divided into groups according to the presence or absence of VS. Comparisons were performed with the Student's test, the Mann–Whitney test, the Kruskal–Wallis test or Fisher's exact test, as appropriate. Spearman's method was used to assess linear correlations. Spearman's coefficient was calculated for the correlation between the brachial artery diameter on one hand and the diastolic arterial pressure, HR, fluid balance and norepinephrine dose



1 on the other. An analysis of variance for repeated measures was performed for  
2 intergroup comparisons and for intragroup comparisons at different time points.  
3 Bonferroni's post hoc test for pairwise comparisons was applied as appropriate. In order  
4 to determine predictors for VS, a receiver-operating characteristic curve (ROC) was  
5 generated for the brachial artery diameter and the FMD response before surgery and on  
6 admission to the ICU. All statistical analyses were performed with SPSS® software  
7 (version 24, IBM® SPSS®). The threshold for statistical significance was set to  $p < 0.05$ .  
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## Results

Thirty patients were included in the study (Figure 1). Two patients were excluded because of incomplete data (Figure 1), and so the final analysis comprised 28 patients. No patient had norepinephrine administration at ICU admission when measurements were performed. Of these 28 patients, 11 (39%) had further developed VS and had been treated with norepinephrine. The VS and non-VS groups did not differ greatly with regard to demographic and surgical data (Table 1). On admission to the ICU, only the HR was higher in the VS group ( $90 \text{ bpm} \pm 13$ ) than in the non-VS group ( $78 \text{ bpm} \pm 14$ ;  $p=0.015$ ) (Table 2).

### *Differences in the brachial artery diameter and the FMD response (Table 2 and Figure 2)*

Before cardiac surgery, the VS and non-VS groups did not differ in terms of the mean  $\pm$  SD brachial artery diameter ( $41 \text{ mm} \pm 12$  and  $39 \text{ mm} \pm 12$ ; respectively;  $p=0.654$ ). The time course of the change in brachial artery diameter differed when comparing the VS and non-VS groups because the diameter decreased significantly ( $p<0.05$ ) in non-VS patients. Hence, the mean  $\pm$  SD brachial artery diameter at ICU admission was higher in the VS group than in the non-VS group ( $39 \text{ mm} \pm 7$  and  $30 \text{ mm} \pm 8$ , respectively;  $p=0.002$ ) (Table 2).

Likewise, the VS and non-VS groups did not differ in terms of the mean  $\pm$  SD FMD (expressed as a percentage) before cardiac surgery. The time-course of the FMD response differed in the two groups because the value at ICU admission was higher in the VS group than in the non-VS group ( $42\% \pm 8$  and  $31\% \pm 1$ , respectively;  $p=0.014$ ) (Table 2).

### *Correlations between brachial artery diameter and hemodynamic parameters*

At ICU admission, the brachial artery diameter was not correlated with the DAP ( $r=0.007$ ;  $p=0.725$ ), SAP ( $r=0.190$ ;  $p=0.332$ ), SVRi ( $r=0.014$ ;  $p=0.944$ ), HR ( $r=0.192$ ;

1 p=0.327), cardiac index ( $r=0.112$ ;  $p=0.571$ ), fluid balance ( $r=0.243$ ;  $p=0.212$ ) or the  
2  
3 norepinephrine dose ( $r=0.219$ ;  $p=0.263$ ).

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6 ***The predictive value of the brachial artery diameter and the FMD response (figure 3)***  
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10 The artery diameter before surgery was not predictive of VS (AUC [95% confidence  
11 interval (CI)] = 0.551 [0.335–0.766];  $p=0.655$ ) (Figure 2). Likewise, the FMD before  
12 surgery did not predict VS (AUC [95%CI] = 0.529 [0.314–0.745];  $p=0.796$ ).  
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17 The artery diameter on admission to the ICU predicted VS with an AUC [95%CI] of  
18 0.850 [0.705–0.995];  $p=0.002$ ). A cut-off of 31.2 mm gave a sensitivity of 91% [78–  
19 100], a specificity of 77% [42–100], a positive likelihood ratio of 6.1, negative  
20 likelihood ratio of 0.15, a positive predictive value of 95, and a negative predictive  
21 value of 67.  
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28 The FMD response on ICU admission predicted VS with an AUC [95%CI] of 0.755  
29 [0.56 - 0.95] ( $p=0.047$ ). A cut-off of 34% gave a sensitivity of 64% [56–100], a  
30 specificity of 60% [42-100], a positive likelihood ratio of 6.1, a negative likelihood ratio  
31 of 0.15, a positive predictive value of 95, and a negative predictive value of 67.  
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## Discussion

The present results demonstrated that (i) the preoperative brachial artery diameter and FMD did not differ between patients with vs. without postoperative VS, (ii) the postoperative change in brachial artery diameter and the FMD response differed between patients with vs. without postoperative VS, (iii) brachial artery diameter and the FMD response were higher after surgery in VS patients than in non-VS patients, and (iv) the brachial artery diameter and the FMD response after surgery were predictive of VS.

The novelty of our results is that FMD and brachial artery diameter at ICU admission are associated with a clinical outcome such as vasoplegic syndrome. In our study, patients who developed vasoplegic syndrome have a different time course profile for brachial artery diameter and FMD after surgery. Our results might explain two studies that have shown contrasted results. In patients undergoing aortic valvular replacement, an increase of brachial artery diameter and two profiles of FMD responders were found after surgery (12). In contrast, Sangalli et al have shown a decrease of FMD response after cardiac surgery (13). The authors of both studies did not evaluate association with clinical outcomes. Furthermore, we observed an increase in brachial artery diameter and the FMD response on admission to ICU in patients who subsequently developed VS. Vasoplegic syndrome is complex, and may involve several mechanisms. This observation may reflect a preclinical disturbance of vasomotor tone related to factors involved in the pathogenesis of VS.

The changes in brachial artery diameter and the FMD response observed here may be due to alterations in vasomotor tone through impairments of the NO pathway. NO is produced by constitutive NO synthase (cNOS) and/or by inductive NO synthase (iNOS) in a wide variety of perturbed conditions. The effects of NO depending on the NOS isoform; NO has beneficial effects when produced by cNOS and harmful effects when produced by iNOS (14). Shabeeh et al. demonstrated that inhibition of NOS in healthy subjects is associated with an alteration in the regulation of blood pressure and HR (15). Furthermore, iNOS is overexpressed under stressed conditions (16, 17). These mechanisms produce an elevated local concentration of NO and lead to the release of inflammatory substances (18). This type of situation is common after cardiac surgery

1 with cardiopulmonary bypass, and may explain the positive results of blue methylene  
2 administration on the incidence and severity of vasoplegia (19, 20).

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4 Lanzarone et al have reported a change between NO release by continuous-flow  
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6 cardiopulmonary bypass or by pulsatile-flow (7). This alteration may be due to a  
7 decrease of cNOS activity, explaining the constant decrease in the FMD response and  
8 the brachial artery diameter in non-vasoplegic patients (21-23). In our study, a higher  
9 brachial artery diameter at a given blood pressure may reflect an increase in regional  
10 blood flow and a decrease in systemic vascular resistance (Table 2). This phenomenon  
11 may be related to NO production by iNOS in patients who will develop VS. A higher  
12 HR might reflect the underlying inflammatory response with NO dysregulation (15).  
13 Effects related to thermogenic homeostasis can be ruled out because the two study  
14 groups did not differ significantly with regard to the body temperature.  
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25 Our study had some limitations. In the absence of literature data collected in the same  
26 setting, we designed a prospective, observational pilot study with a conveniently sized  
27 sample of 30. Nevertheless, this relatively small sample size is similar to those used in  
28 previous studies on this topic (7, 13), and its sufficient to demonstrate an AUC greater  
29 than 0.80 with a power of 80% and an alpha risk of 0.05. The optimal definition of VS  
30 is subject to debate; we used the definition most frequently used in recent studies (9,  
31 10). Vascular resistance tends to be lower in our findings. Those observations fit well  
32 with the definition of VS. There were no cases of cardiac failure in our study  
33 population, and the administration of dobutamine was never required. Our results for  
34 the FMD response and artery diameter are in line with the literature data. Dedichen et  
35 al. recorded diameter values of about 40 mm (23). In Tataka et al.'s study, the mean  
36 diameter was also around at 40 mm, and variations in the FMD response were even  
37 higher (around 50%) than in our study (around 35%) (12, 24). In our study, the FMD  
38 measurements were all performed by the same investigator and the reproducibility was  
39 improved by marking the measurement site on the arm. We excluded two patients with  
40 incomplete datasets for the FMD response. Daily assessment of the FMD response at  
41 the bedside may be problematic, as it requires several clinical conditions to be met (9).  
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## Conclusion

Our study demonstrated that the change in brachial artery diameter and the FMD response after surgery differed when comparing patients with and without postoperative VS. The patients who developed VS display an increase in the brachial artery diameter and the FMD response following cardiac surgery with cardiopulmonary bypass. The brachial artery diameter and the FMD response on admission to the ICU were predictive of VS. Vasoplegic syndrome may be associated with an alteration in the endothelium's vasomotor response to NO.

## List of abbreviations

FMD: flow mediated dilatation; HR: heart rate; ICU: intensive care unit; MAP: mean arterial pressure; NO: nitric oxide; VS: vasoplegic syndrome.

## Declarations

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None declared.

### Availability of data and materials

The dataset generated and/or analysed during the present study is not publicly available, owing to patient-related confidentiality, but it is available from the corresponding author on reasonable request.

### Authors' contributions

O.AA: study design, patient recruitment, data collection and writing the first draft of the manuscript, final approval.

L.M: patient recruitment, final approval.

M.G: patient recruitment, final approval.

S.B: drafting, final approval.

1 A.BA: patient recruitment, final approval.

2 T.C: revision, final approval.

3 H.D: revision, final approval.

4 K.S: revision, final approval.

5 P.GG: study design, patient recruitment, data collection and drafting, revision, final  
6 approval.

7 E.L: drafting, revision, final approval.

#### 8 **Authors' information**

9 Not applicable.

#### 10 **Ethics approval and consent to participate**

11 This study was approved by the institutional review board of Amiens Hospital  
12 University (Amiens, France). Written informed consent was obtained from each patient  
13 or family member before enrollment.

#### 14 **Competing interests**

15 The authors declare that they have no competing interests.

#### 16 **Consent for publication**

17 Not applicable.

#### 18 **Declaration of interest**

19 None declared.

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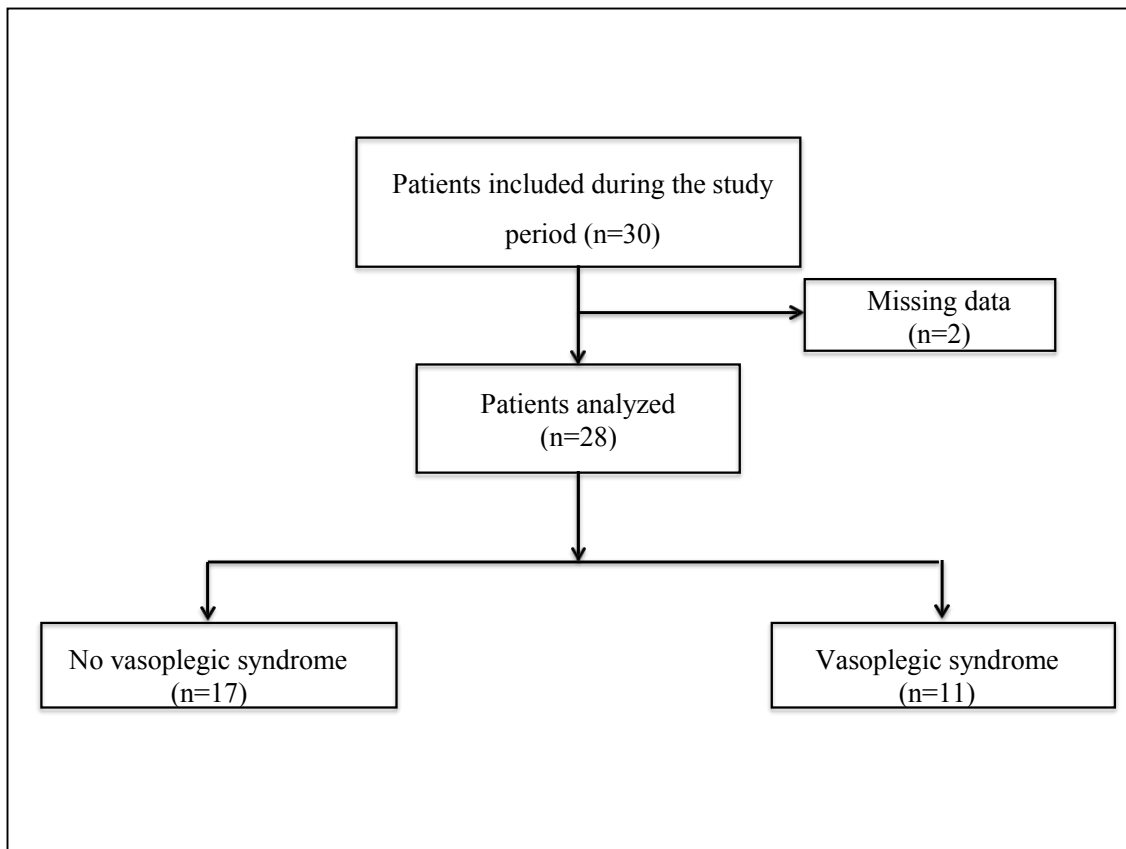
**Table 1 Demographic and surgical data.** Data are expressed as mean  $\pm$  standard deviation, median [25<sup>th</sup>-75<sup>th</sup>] or number (%). BMI: body mass index; CABG: coronary artery bypass surgery; CBP: cardiopulmonary bypass; LVEF: left ventricular ejection fraction; VS: vasoplegic syndrome. Comparisons were performed with a Student/Mann-Whitney test or a chi-squared/Fisher's exact test, as appropriate.

	<b>No VS (n=17)</b>	<b>VS (n=11)</b>	<b>P value</b>
Age (years)	68 $\pm$ 11	63 $\pm$ 13	0.323
Gender (male, %)	10 (58)	8 (73)	0.689
BMI (mg.kg <sup>-2</sup> )	26.8 $\pm$ 3.8	26.5 $\pm$ 6.0	0.881
Euroscore II (%)	1.86 $\pm$ 1.20	1.31 $\pm$ 0.68	0.132
Surgery (n, %)			
CABG	6 (35)	5 (46)	0.442
valve replacement	7 (41)	4 (36)	
combined	2 (12)	2 (18)	
other (ascending aorta)	2 (12)	0 (0)	
Medical history, (n, %)			
diabetes	12 (71)	8 (73)	1.000
hypertension	7 (41)	7 (64)	0.246
dyslipidaemia	12 (71)	8 (73)	1.000
smoker	15 (88)	6 (55)	0.076
coronary disease	12 (71)	5 (46)	0.248
Preoperative medication (n, %)			
Beta blocker	10 (59)	8 (72)	0.689
Angiotensin converting enzyme inhibitor	10 (59)	4 (36)	0.440
Statin	10 (59)	8 (72)	0.689
Furosemide	4 (24)	2 (18)	1.000
Aspirin	8 (47)	5 (46)	1.000
Calcium blocker	2 (12)	2 (18)	1.000
LVEF (%)	64 $\pm$ 9	61 $\pm$ 11	0.677
Haematocrit (%)	39.6 $\pm$ 4.3	39.8 $\pm$ 3.7	1.000
Creatinine level ( $\mu$ mol.l <sup>-1</sup> )	66 [58-79]	69 [60-78]	0.323
<i>Peroperative data</i>			
Duration of CBP (min)	107 $\pm$ 38	117 $\pm$ 32	0.517
Duration of aortic clamping (min)	74 $\pm$ 27	87 $\pm$ 28	0.378
Total heparin dose (UI.kg <sup>-1</sup> )	313 $\pm$ 37	307 $\pm$ 60	0.788
Total protamin dose (UI.kg <sup>-1</sup> )	257 $\pm$ 37	266 $\pm$ 76	0.670
Red blood cell transfusion (n, %)	1 (6)	2 (18)	0.543
Total fluid expansion (ml)	1000 [1000-1750]	1500 [1000-2000]	0.289

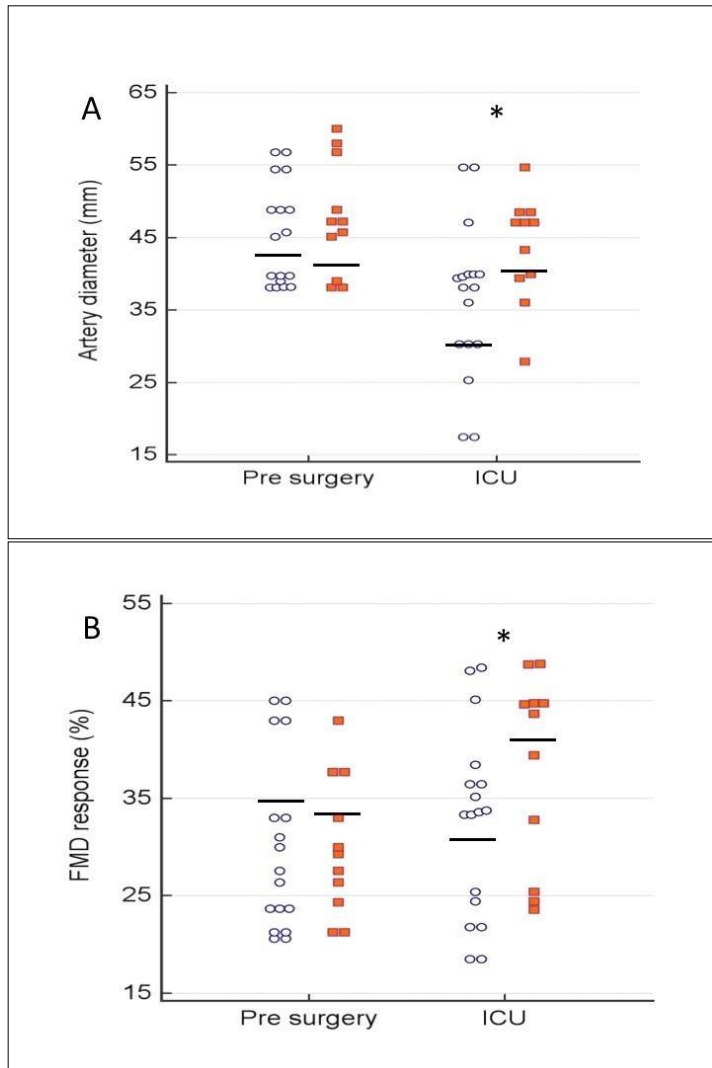
**Table 2 Characteristics at ICU admission and 48 postoperative course data.** Data are expressed as mean  $\pm$  SD or numbers (percentage). H0: at ICU admission; LVEF: left ventricular ejection fraction; FMD: flow-mediated dilatation. HR, heart rate in bpm; MAP Mean arterial pressure in mmHg; DAP Diastolic arterial pressure in mmHg; LVEF Left ventricular ejection fraction; ICU Intensive care medicine; FMD flow mediated dilatation. Comparisons were done by Mann Whitney test or chi-2/Fischer exact test. Diameter and FMD comparisons were done by 2 way ANOVA test.

	No vasoplegic syndrome (N= 17)	Vasoplegic syndrome (N=11)	P value
Temperature ( $^{\circ}$ C) at H0	36.5 $\pm$ 0.7	36.5 $\pm$ 0.7	0.306
HR at H0	78 $\pm$ 14	90 $\pm$ 13	0.015
MAP at H0	82 $\pm$ 15	77 $\pm$ 14	0.404
DAP at H0	65 $\pm$ 11	61 $\pm$ 13	0.430
SvO2 (%) at H0	69 $\pm$ 9	75 $\pm$ 8	0.100
Dobutamine at H0	0	0	-
Norepinephrine at H0	0	0	-
Lactate level at H0 (mmol/l)	1.5 $\pm$ 0.6	1.3 $\pm$ 0.3	0.813
Hematocrit (%)	34 $\pm$ 4	35 $\pm$ 5	0.487
Albumin level (mg/l) at H0	26 $\pm$ 4	27 $\pm$ 5	0.487
LVEF (%)	50 $\pm$ 9	45 $\pm$ 11	0.532
<i>During ICU stay</i>			
Cumulative norepinephrine (mg/kg)	0	0.48 $\pm$ 0.22	-
Cumulative fluid challenge (ml)			
Cumulative diuresis (mg/kg/h)	1.2 $\pm$ 0.7	0.9 $\pm$ 0.4	0.512
ICU stay (days)			
Artery diameter before FMD (mm)			
Base	41 $\pm$ 12	39 $\pm$ 12	0.654
H0	30 $\pm$ 8	39 $\pm$ 7	0.002
FMD (%)			
Base	3.5 $\pm$ 0.2	3.4 $\pm$ 0.1	0.796
H0	3.1 $\pm$ 0.1	4.2 $\pm$ 0.8	0.014

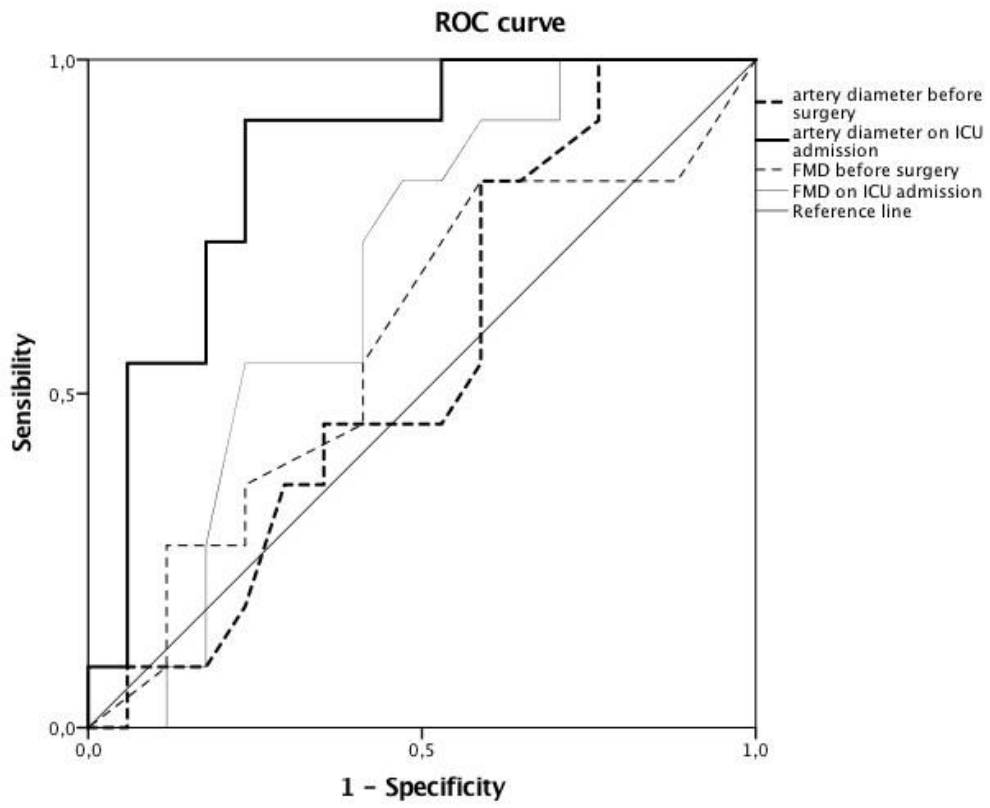
Figure 1. Flow chart.



**Figure 2. Brachial artery diameter (panel A) and FMD (panel B) before surgery and after surgery (on admission to the intensive care unit (ICU)); \* p<0.005 when comparing the non-VS and VS groups.**



**Figure 3. ROC curves for predicting VS. FMD: flow-mediated dilatation response and artery diameter before and after cardiac surgery.**



## **b. L'analyse du couplage ventriculo-artériel prédit les effets hémodynamiques de la noradrénaline chez des patients atteints de syndrome vasoplégique**

Le syndrome vasoplégique et sa réponse hémodynamique à un traitement par noradrénaline font l'objet d'un nombre important d'études hémodynamiques descriptives. Ces études ont confirmé les concepts hémodynamiques de Franck-Starling et Guyton et les effets pharmacologiques connus de la noradrénaline (89-93). Ainsi, le syndrome vasoplégique est associé à une hypotension artérielle avec des résistances vasculaires périphériques abaissées et un débit cardiaque conservé ou augmenté. L'administration de noradrénaline restaure la pression artérielle avec un effet inconstant sur le débit cardiaque (soit celui-ci augmente, soit celui-ci baisse). A la lecture de la littérature, une réflexion est portée par l'auteur de cette thèse sur deux points :

1. la majorité des études cliniques étudient des patients avec de nombreux biais : patients inclus souvent réanimés, association de plusieurs catécholamines (dobutamine, adrénaline, milrinone...), exploration par modification des posologies de noradrénaline.
2. l'interprétation hémodynamique est prisonnière des modèles utilisés pour la décrire (Franck-Starling, Guyton).

Cette réflexion appuyée par des observations cliniques quotidiennes a abouti à la mise en place d'une étude observationnelle utilisant une approche hémodynamique complémentaire des approches basées sur des modèles pression-débit : l'analyse du couplage-ventriculo artériel. Par ailleurs, ce travail inclut des patients présentant une hypotension artérielle persistante jugée comme traduisant un syndrome vasoplégique avant la mise en place du traitement par noradrénaline et en l'absence d'autres catécholamines.

Une description des effets cardio-vasculaires de la noradrénaline ne peut qu'améliorer notre compréhension de la physiopathologie des insuffisances circulatoires aiguës et nous aider à prédire plus efficacement les effets hémodynamiques de la noradrénaline, et éventuellement définir de nouvelles cibles thérapeutiques qui pourraient améliorer le devenir des patients. Compte tenu des effets cardiovasculaires multiples de la noradrénaline, il serait intéressant d'identifier



quel paramètre hémodynamique est capable de prédire une augmentation de la pression artérielle et du débit cardiaque. Étant donné que les systèmes ventriculaire et artériel fonctionnent simultanément, le couplage ventriculo-artériel détermine le volume d'éjection systolique et la pression d'éjection (c'est-à-dire la pression artérielle). Ainsi, nous avons émis l'hypothèse que l'analyse du couplage ventriculo-artériel peut permettre une meilleure caractérisation de l'état cardiovasculaire et la prédictibilité des changements de volume d'éjection systolique avec l'administration de noradrénaline. A cette fin, 30 patients en post-opératoire de chirurgie cardiaque pour lesquels un traitement par noradrénaline était instauré ont été inclus. La mesure du couplage ventriculo-artériel était réalisée par une technique non-invasive échocardiographique.

Le résultat principal de l'étude est que l'amélioration du couplage ventriculo-artériel lors de l'administration de la noradrénaline est associée à une amélioration du VES (donc du Dc). En post-opératoire de chirurgie cardiaque, les élastances artérielles et ventriculaires sont anormales chez de nombreux sujets présentant une hypotension artérielle persistante. L'effet prédominant de la noradrénaline sur les fonctions cardiaques et vasculaires dépend de l'état de base cardio-vasculaire. Cet état cardio-vasculaire est mieux décrit par l'analyse du couplage ventriculo-artériel que par des paramètres (débit cardiaque, résistances vasculaires périphériques) analysés indépendamment l'un de l'autre. La noradrénaline peut avoir principalement des effets inotropes en cas de dysfonction ventriculaire gauche et principalement des effets vasoconstrictifs en cas de dysfonctionnement artériel.

**Ventriculo-arterial coupling analysis predicts the hemodynamic response to  
norepinephrine in hypotensive postoperative patients: a prospective observational study.**

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**Authors' contributions**

Data acquisition: PGG; Analysis and interpretation: PGG, DL; Drafting of the manuscript for  
important intellectual content: PGG, DL, EL, HD, SK. All authors read and approved the  
manuscript.

**Competing interests**

The authors declare that they have no competing interests.

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## Abstract

**Objectives:** The objectives of the present study were to evaluate, in patients with persistent arterial hypotension in the immediate post-cardiac surgery period, the effects of norepinephrine infusion on ventriculo-arterial coupling (V-A coupling), its determinants: arterial elastance ( $E_A$ ) and ventricular elastance ( $E_{es}$ ), and to test the ability of  $E_A/E_{es}$  ratio to predict stroke volume (SV) increases.

**Design:** Prospective observational study

**Setting:** Cardiac-vascular surgical ICU

**Patients:** Twenty-eight postoperative cardiac surgery patients, in whom physicians decided to administer NE infusion were included.

**Measurements and main results:** Arterial pressure, stroke volume index (SVi), cardiac index (CI), indexed total peripheral resistance (TPRi), arterial compliance ( $C_A$ ),  $E_A$ , and  $E_{es}$ , were measured before and after NE infusion. We estimated V-A coupling by the  $E_A/E_{es}$  ratio and defined SV responders by a SV increase  $\geq 15\%$ . Twenty-two of the 28 **subjects** had altered VAC (1.87 (1.57-2.51) vs 1.1 (1-1.18)). Fifteen (54%) of the 28 **subjects** were SV responders. At baseline, SV responders had similar arterial pressure, higher TPRi,  $E_A$ ,  $E_A/E_{es}$  ratio (2.21 (1.69-2.89) vs 1.33 (1.1-1.56);  $p < 0.05$ ) and lower  $C_A$ , TPRi and CI. Norepinephrine significantly increased arterial pressure in all **subjects**. In SV responders, norepinephrine increased  $E_A$ ,  $E_{es}$ , CI, and improved  $E_A/E_{es}$  coupling. The baseline  $E_A/E_{es}$  ratio predicted SV responsiveness (area under the curve [95% confidence interval]: 0.87 [0.71–1];  $p < 0.0001$ ).

**Conclusions:** In patients with arterial hypotension norepinephrine increased  $E_{es}$  and  $E_A$ . The effects of norepinephrine on SV depend on baseline V-A coupling. Although NE infusion corrects arterial hypotension in all **subjects**, increase of SV occurred only in **subjects** with altered V-A coupling.

**Keywords:** ventriculo-arterial coupling, arterial hypotension, surgical intensive care,  
norepinephrine

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## Introduction

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2 Because norepinephrine is the cornerstone of acute circulatory failure treatment in critically ill  
3 patients, an abundant literature has been published on this topic (1, 2). Actually, most of the  
4 literature in humans has evaluated norepinephrine and its macro-hemodynamic effects  
5 according to a “cardio-centric” pressure/outflow model (i.e Guyton, Franck Starling) (3-6).  
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7 This approach has been useful to provide a complex although not complete understanding of  
8 the mechanisms that underlie the effects of norepinephrine, including cardiac surgery patients  
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17 (4).

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19 As a complement to the “cardio-centric” pressure-flow model, several authors have applied a  
20 model that is based on an integrated pressure-volume relationship of left ventricle and  
21 vascular system (7-10). This model is based on measurement of the end systolic ventricular  
22 elastance ( $E_{es}$ ) and arterial elastance ( $E_A$ ) (7-10).  $E_{es}$  is an integrated measure of LV systolic  
23 performance derived from the complex association between the inotropic efficiency and the  
24 functional, structural and geometric characteristics of the left ventricle (11).  $E_A$  describes the  
25 arterial load in an integrated manner that takes into account total peripheral vascular  
26 resistance (TPR), total arterial compliance ( $C_A$ ), characteristic impedance and systolic and  
27 diastolic time intervals (11). Ventriculo-arterial coupling (V-A coupling) is defined by the  
28 ratio of  $E_A/E_{es}$  (10). V-A coupling model was widely used in cardiology to describe  
29 pathophysiology and understand the effect of cardiologic therapeutics (11-14). The clinical  
30 relevance of this model is based on the fact that  $E_A/E_{es}$  predicts outcomes independently from  
31 other parameters in patients with cardiovascular diseases (15).

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51 At the bedside, the cardio-vascular effects of norepinephrine infusion are difficult to  
52 predict. Studies demonstrated a systematic increase of arterial pressure through  
53 vasoconstrictive effects, regardless of the aetiology (1-6). Nevertheless these effects were  
54 inconsistent on cardiac function and cardiac output (CO) (3-6). One study in resuscitated  
55 normotensive postoperative patients demonstrated that norepinephrine increase preload, thus

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CO (4). In this respect, respiratory stroke volume variation (SVV) was predictive of CO changes (4).

A description of the cardiovascular effects of NE may improve our understanding of the pathophysiology of hemodynamic states, and help physicians at the bedside to more reliably predict the effects of NE and possibly define new therapeutic targets that could improve patient outcomes. In view of the multiple cardiovascular effects of norepinephrine it would be interesting to identify which parameter is able to predict an increase both in arterial pressure and stroke volume (SV). Given that the ventricular and arterial systems operate simultaneously, V-A coupling determines the SV and the ejection pressure (i.e. the arterial blood pressure). Thus, we hypothesized that V-A coupling may enable better characterization of the cardiovascular state, and predictability of SV changes with norepinephrine infusion.

The objective of this study was to demonstrate the ability of  $E_A/E_{es}$  ratio to predict an increase of SV with norepinephrine infusion in hypotensive patients while intubated and sedated in the few hours following cardiac surgery.

## METHODS

### *Patients*

The study objectives and procedures were approved by the local ethics committee (*Comité de Protection des Personnes Nord-Ouest II* CHU - Place V. Pauchet, 80054 AMIENS Cedex 1).

All subjects received written information about the study and provided their consent to participate. The present manuscript was drafted in compliance with the STROBE checklist for cohort studies (16).

This prospective, observational study was performed in the Amiens University Hospital cardiovascular and thoracic ICU. Inclusion criteria were patients over the age of 18 years, under controlled positive-pressure ventilation and sedated, for whom the physician decided to **infuse norepinephrine during the six first hours following admission to the ICU**. The indications for norepinephrine were persistent arterial hypotension (systolic arterial pressure less than 100 mmHg and/or mean arterial pressure less than 65 mmHg) despite fluid therapy (17). Exclusion criteria were spontaneous ventilation, permanent arrhythmia, cardiac conduction disorders, presence of a pacemaker (or requirement for use of temporary pacemaker), dobutamine or epinephrine infusion, poor echogenicity and right heart dysfunction.

### *Haemodynamic parameters*

Transthoracic echocardiography (CX50 Ultrasound System and an S5-1 Sector Array Transducer, Philips Medical System, Suresnes, France) was performed by a physician blinded to the results of the study. Left ventricular ejection fraction (LVEF), end-systolic volume (ESV), and end-diastolic volume (EDV) were calculated using Simpson's method on a four-chamber view. The diameter of the left ventricular outflow tract (LVOT) was measured on a long-axis parasternal view at the time of patient inclusion. The aortic velocity-time integral

1  
2 (VTIAo), pre-ejection time and systolic time were measured with pulsed Doppler on a five-  
3 chamber apical view. Stroke volume (SV; mL) was calculated as  $VTIAo \times Aortic\ area$  and was  
4 expressed as indexed SV ( $SV_i$ ) =  $SV/body\ surface\ area\ (ml.m^{-2})$ . Cardiac index (CI) ( $l.min^{-1}$   
5  $.m^{-2}$ ) was calculated as  $SV_i \times heart\ rate\ (HR)$ . Respiratory variation of SV (SVV) was  
6 calculated as:  $SVV = (SV_{max} - SV_{min}) / ((SV_{max} + SV_{min}) / 2) * 100$ . Mean echocardiographic  
7 parameters were calculated from the average over five consecutive cardiac cycles, and  
8 analysed retrospectively.  
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### 15 ***Left ventricular end-systolic elastance, arterial elastance, ventriculo-arterial coupling***

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18  $E_{es}$  was estimated at the bedside using the non invasive single beat method described by Chen  
19 *et al.* (18). This method does not assume that the volume axis intercept of end systolic  
20 pressure volume relation is at the origin of the diagram (0; 0) but can be extrapolated to  
21 intersect the volume axis at the point  $V_0 ; 0$  (19).  
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31  $E_A$  was estimated by using the formula  $E_A = 0.9 * systolic\ arterial\ pressure\ (SAP) / SV$  (20).

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mean arterial pressure (MAP), diastolic arterial pressure (DAP), central venous pressure (CVP),  $TPR_i$ ,  $SV_i$ , CI, pre-ejection time and systolic time interval, PPV and arterial/venous blood gas levels were obtained. After 15 minutes of hemodynamic stability defined as a variation of MAP less than 10% with norepinephrine infusion, a second set of measurements was recorded (4). All patients had been sedated by continuous infusion of propofol, and were fully adapted to volume-controlled mode with a tidal volume ( $V_t$ ) set at 7-9 ml.kg<sup>-1</sup> of ideal body weight, and a positive end-expiratory pressure (PEEP) of 5-8 cmH<sub>2</sub>O. **Ventilator settings and propofol rate were not modified during the study period.**

### ***Statistical analysis***

A sample of thirty patients was calculated to be sufficient to demonstrate that  $E_A/E_{es}$  ratio predict an increase of SV in response to norepinephrine treatment with an AUC greater than 0.80, a power of 80% and an alpha risk of 0.05. The coefficient of variation (CV), precision and least significant change (LSC) for  $E_{es}$  were calculated on ten patients. The CV is a statistical measure of the dispersion of  $E_{es}$  data points. The LSC is the least amount of  $E_{es}$  change that can be considered to be statistically significant, i.e. the minimum percentage change between two successive measurements that can be considered not to be due to random error and therefore representing a real change in  $E_{es}$  in ten patients. The CV was 7.7% ± 0.6 and the LSC was 10.9% ± 0.8. The distribution of the variables was assessed using a Shapiro-Wilk test. Data are expressed as the proportion (%), mean ± standard deviation (SD) or median (interquartile range), as appropriate. Patients were classified according to the effect of norepinephrine on  $SV_i$  (4). A SV responder was defined as a greater than 15% increase in  $SV_i$  (23). The non-parametric Wilcoxon rank sum test, Student's paired t test, Student's t test, and the Mann-Whitney test were used to assess statistical significance, as appropriate. **A receiver-operating characteristic curve was established for SVV,  $TPR_i$ ,  $SV_i$ , and  $E_A/E_{es}$  ratio to predict a greater than 15% increase in SV (4). The ROC curves were compared using the DeLong**

test. The threshold for statistical significance was set to  $p < 0.05$ . SPSS® software (version 24, IBM, New York, USA) was used for statistical analysis.

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## RESULTS

Of thirty patients included in the study, two were excluded. The study is based on 28 subjects

(Figure 1) who had undergone cardiac surgery (Table 1). None of the subjects were treated with epinephrine or dobutamine during the study period. Subjects' demographic characteristics are presented in Table 1. At baseline, there were no differences between SV responder and SV non-responder subjects. The prevalence of uncoupled subjects did not differ according to the type of surgery ( $p=0.541$ ), therefore allowing pooled analysis.

### Effects of norepinephrine infusion on hemodynamic parameters in the overall

#### population (n=28)

At baseline, median  $E_A$  was 1.69 (1.39-2.24) mmHg.ml<sup>-1</sup>, median  $E_{es}$  was 1.1 (0.65-1.42) mmHg.ml<sup>-1</sup>, median  $E_A/E_{es}$  ratio was 1.69 (1.34-2.43), and 22 (79%) of the 28 subjects were classified as uncoupled (i.e.,  $E_A/E_{es} > 1.36$ ). Values for  $E_A$ ,  $E_{es}$  and  $E_A/E_{es}$  ratio did not differ between men and women ( $P > 0.05$ ). In the study population as a whole, norepinephrine infusion induced increases in arterial pressure, CVP, SVi, CI, TPRi,  $E_A$ ,  $E_{es}$  (Table 2).

### Effects of norepinephrine infusion on hemodynamic parameters according to stroke volume response

Fifteen (54%) of the 28 subjects were classified as SV responders. Baseline TPRi, and  $E_A/E_{es}$  were higher, but SVi, CI, and LVEF were lower in SV responders compared to SV non-responders (Table 2). In SV responders, norepinephrine infusion induced increases in arterial pressure, SVi, CI, TPRi,  $E_A$ ,  $E_{es}$ , and decreases in  $C_A$ ,  $E_A/E_{es}$  ratio (Table 2, Figure 2). In SV non-responders, norepinephrine infusion induced increases in arterial pressure, TPRi,  $E_A$ ,  $E_{es}$ , and decreases in  $C_A$  (Table 2, Figure 2).

Changes in  $E_A$  and TPRi were greater in SV non-responders than in SV-responders (41% (22-

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61) vs 15% (1-21),  $p=0.0001$  and 41% (18-60) vs 8% (0-17),  $p=0.0001$ ). Changes in  $E_{es}$  did not differ between the two groups of patients (29% (13-60) vs 25% (12-61),  $p=0.821$ ). Changes in  $E_A/E_{es}$  ratio differed between SV-responders and SV non-responders (16% (23-0) vs 1% (0-22),  $p=0.010$ )).

### **Predictability of $E_A/E_{LV}$ ratio, TPRi, SVi, and SVV to discriminate SV increases with norepinephrine infusion (Figure 3)**

Baseline  $E_A/E_{es}$  ratio was predictive of SV responsiveness with an AUC of 0.87 (95%CI: 0.72 to 0.98,  $p=0.001$ ). The cut-off was 1.5 with a sensitivity of 94% [68-100], a specificity of 77% [46-95], a positive likelihood ratio of 4.07, a negative likelihood ratio of 0.087, a positive predictive value of 82% and a negative predictive value of 91%.

With an AUC of 0.72 (95%CI: 0.54 to 0.9,  $p=0.040$ ), SVi fairly predicted SV responsiveness. With an AUC of 0.73 ((95%CI: 0.55 to 0.93,  $p=0.032$ ), TPRi fairly predicted SV responsiveness. With an AUC of 0.66 (95%CI: 0.46 to 0.83,  $p=0.135$ ), SVV did not predict SV responsiveness. The AUC of  $E_A/E_{es}$  ratio was greater than those of SVi and TPRi ( $p<0.05$ ).

## DISCUSSION

The main result of the study is that norepinephrine improvement in V-A coupling was associated to SV response in cardiac postoperative hypotensive subjects. Both  $E_{es}$  and  $E_A$  are abnormal in many subjects with persistent arterial hypotension despite volume expansion. Most of subjects presented abnormal  $E_A/E_{es}$  ratio, mainly due to high  $E_A$ , (low  $C_A$ , high  $TPR_i$ ) and low  $E_{es}$ . Baseline  $E_A/E_{es}$  has the highest AUC ROC to predict SV increase.

The results of our study confirm previous ones (6, 13, 14) but they add a new perspective on the cardiovascular effects of norepinephrine. The predominant effect of norepinephrine on myocardial and vascular functions may depend on the cardiovascular baseline state.

Cardiovascular state was better described by V-A coupling than by flow parameters (CO,  $TPR_i$ ) analysed independently from each other. Norepinephrine may have mainly inotropic effects in case of left ventricular dysfunction and mainly vasoconstrictive effects in case of arterial dysfunction. Correction of either of these parameters results in improvement of V-A coupling.

One clinically relevant question may be why should we consider V-A coupling as a parameter to describe the cardiovascular system and its response to treatment? There are several answers. The first one is that there is strong evidence from the cardiology area that V-A coupling independently predicts outcomes and the response to therapy (24, 25). When applied to the context of critical care and cardiac surgery patients, it is first an extension of these validated concepts. Second, in a patient who is hypotensive despite volume expansion and who receives norepinephrine, the efficacy of this treatment can be classically estimated on two independent levels; (i) increase in arterial blood pressure and SV. None of these parameters differentiated in this study between SV-responders and non responders; (ii) when echocardiography parameters are measured, there are differences that reveal which SV-responders and non-responders patients are different before and after NE infusion;

1 nevertheless, “cardio-centric” parameters (SV) do not allow a thorough understanding of the  
2 mechanisms that explain the differences between SV-responders and non-responders; (iii)  
3 VA-coupling description that integrates HR, SV, ventricular contractility, arterial compliance,  
4 TPR<sub>i</sub> and their interaction explain the mechanisms of the SV-responsiveness. It must be  
5 stressed that E<sub>es</sub> is the only parameter that takes into consideration left ventricular  
6 contractility in a (nearly) load-independent manner (7).

7 Norepinephrine infusion increased E<sub>A</sub> and E<sub>es</sub> but not to the same extent between groups,  
8 resulting in V-A coupling improvement and SV increase in the SV-responders group. We  
9 demonstrated an increase in E<sub>es</sub> in relation to several known pharmacological effects of NE  
10 (activation of alpha- and beta-adrenergic receptors, improvement in coronary perfusion  
11 pressure...) (26-28). On the contrary, the effects of norepinephrine on E<sub>A</sub> may have been  
12 different between the two groups because the hemodynamic response to NE depends on the  
13 baseline vasomotor tone (29). In SV non-responders, the increase in E<sub>A</sub> may be mainly due to  
14 vasoconstrictive effects on resistive component (TPR<sub>i</sub>). Stroke volume did not decrease  
15 because the increase of arterial load was compensated by the increase of E<sub>es</sub>. In SV  
16 responders, E<sub>A</sub> changes may be mostly due to inotropic effects. Norepinephrine did not  
17 change TPR<sub>i</sub> because the values were already high due to sympathetic activation probably  
18 secondary to more altered left ventricular function before infusion of NE (see Table 2) (29).  
19 Thus the E<sub>es</sub> increase was greater than that of E<sub>A</sub> restoring V-A coupling, increasing LVEF  
20 and SV (9). The effects of norepinephrine infusion in SV-responders may not be related to  
21 preload changes because preload variables (EDV, IVC diameter and SVV) did not change  
22 with norepinephrine infusion.

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Comparison of the predictive value of the various hemodynamic parameters shows  
that the E<sub>A</sub>/E<sub>es</sub> ratio had the highest ROC AUC. SVV was not predictive of SV increase  
because SV increase was not associated to preload changes (4). This validates our inclusion  
criteria: patients with persistent arterial hypotension despite volume expansion. The higher

1 predictive value of  $E_A/E_{es}$  ratio is probably due to the fact that this parameter reflects HR, LV  
2 inotropism, SV, TPRi, arterial pressure, and their interactions, reflecting the integrated  
3 physiology of the cardiovascular system, in which the heart and arterial circulation are  
4 coupled. Flow parameters analysed independently from each other (SV, TPRi...) were less  
5 predictive because they do not reflect cardiac and vascular interactions.  
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11 Our results provide a strong incentive to use combined flow and pressure parameters to  
12 evaluate the cardiovascular effects of catecholamines. This approach is an extension of V-A  
13 coupling from the cardiology literature to the post-cardiac surgery period. The results  
14 obtained in this study confirm the importance of an integrated analysis of the cardiac and  
15 vascular system (30, 31).  
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23 Several limitations of our study should be considered. Because we included subjects  
24 operated of different cardiac surgery, reliability of our results can be questioned. We did not  
25 demonstrate any difference of baseline variables (demographic, ICU) between SV responders  
26 and SV non-responders.  $E_{es}$  is a parameter that reflects the functional, structural and  
27 geometric characteristics of the left ventricle (32). V-A coupling represents a parameter of  
28 integrated cardiovascular physiology that is an alteration per-se, probably independent from  
29 the underlying type of heart disease (7, 32). The methods used to calculate  $E_{es}$  and  $E_A$  can be  
30 questioned. We measured  $E_{es}$  by a non-invasive single beat method that is based on a linear  
31 end-systolic pressure-volume relation and a constant volume axis intercept ( $V_0$ ) of the end-  
32 systolic pressure volume relation (18).  $E_{es}$  calculation assumes that the end-systolic pressure-  
33 volume relationship is independent of load and that its slope is linear.  $V_0$  is assumed to be  
34 negligible compared with ESV and to be insensitive change of loading or inotropic conditions  
35 (7). Changes in left ventricular contractility can be due to changes in  $E_{es}$  or  $V_0$ . Although it  
36 can be argued that the estimation of end systolic pressure from the radial artery is not fully  
37 validated, this would only affect the precision of absolute values of  $E_A$  and  $E_{es}$  but not of the  
38  $E_A/E_{es}$  ratio because the error in end systolic pressure would be similar. In this regard, the  
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1 predictive value of the  $E_A/E_{es}$  for increases in SV is valid. We measured  $E_A$  from a radial  
2 artery catheter that certainly differs from aortic pressure, especially in younger patients, but  
3 probably less so in elderly patients, who constituted the majority of **subjects** in our study.  
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5 Nevertheless, radial artery pressure has been demonstrated to provide a good estimation of  
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7 end-systolic LV pressure (33). Arterial load assessment was based on the two-element  
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9 Windkessel model and integrative simplification, defined by the effective  $E_A$ . More precise  
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11 models have been developed that include arterial input impedance and wave reflection, but  
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13 such measurements would be difficult to perform at the bedside. Despite these limitations,  
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15 non-invasive evaluation of  $E_{es}$  and  $E_A$  were validated against the gold standard method, and  
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17 have been widely used to evaluate the effects of therapeutic interventions (12, 15).  
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## 24 **CONCLUSIONS**

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27 **In conclusion, analysis of V-A coupling allowed better prediction of the SV response to**  
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29 **norepinephrine. The response of the cardiovascular system to norepinephrine depends on left**  
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31 **ventricular contractility, the vascular system and their interactions.** These results could be an  
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33 incentive to assess the cardiovascular effects of norepinephrine in cardiac surgery patients by  
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35 taking into account not only cardiac output and/or blood pressure but also V-A coupling.  
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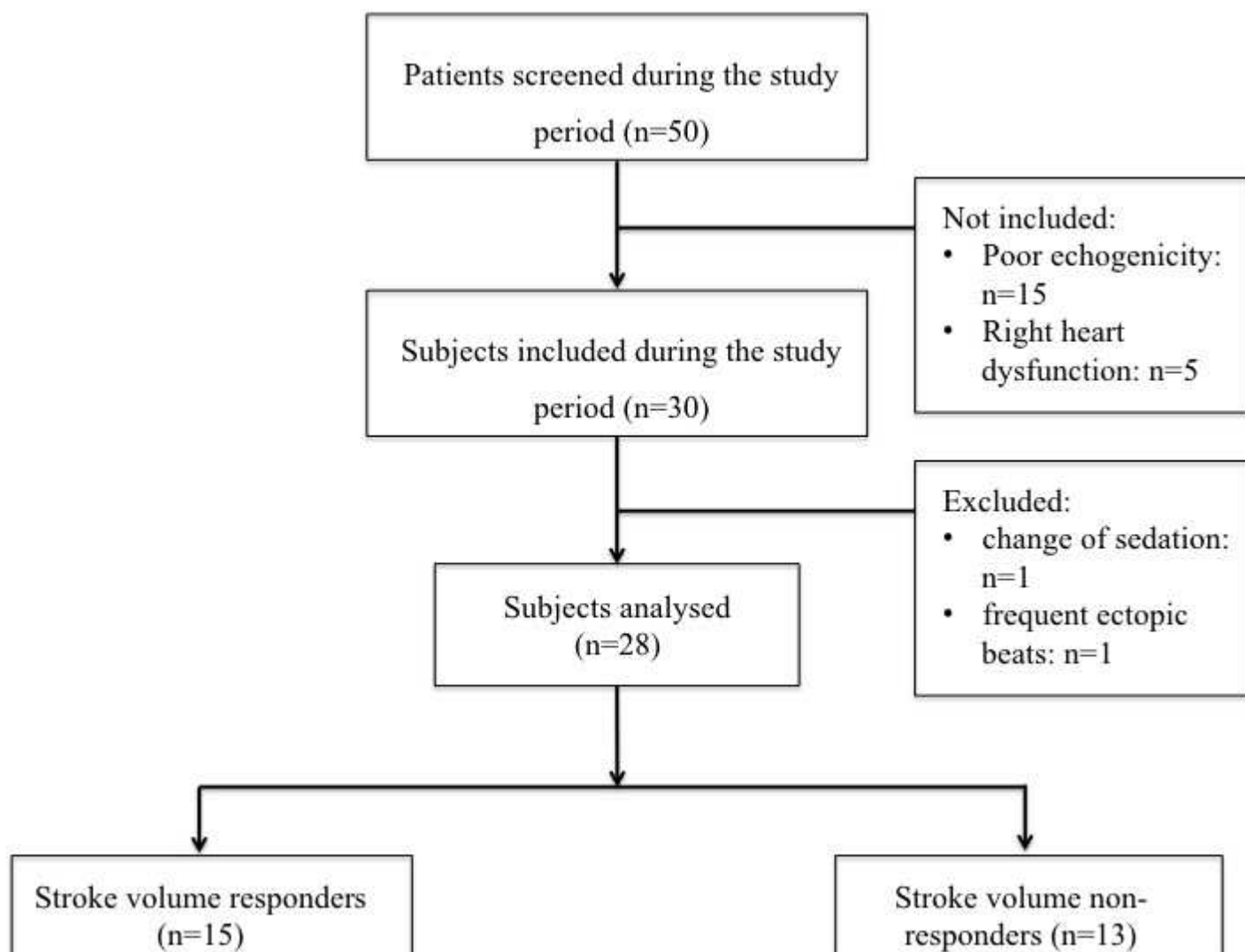
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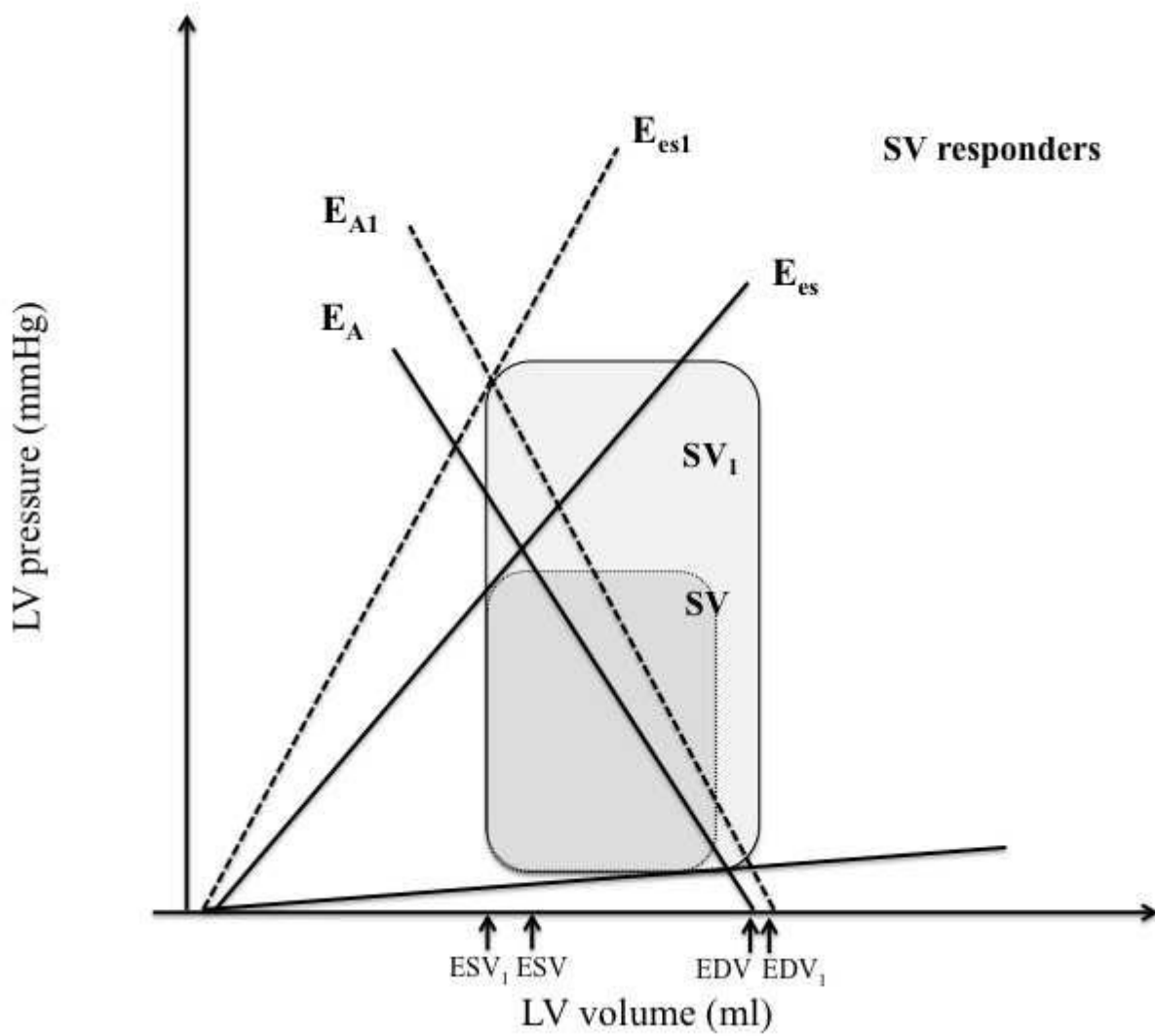
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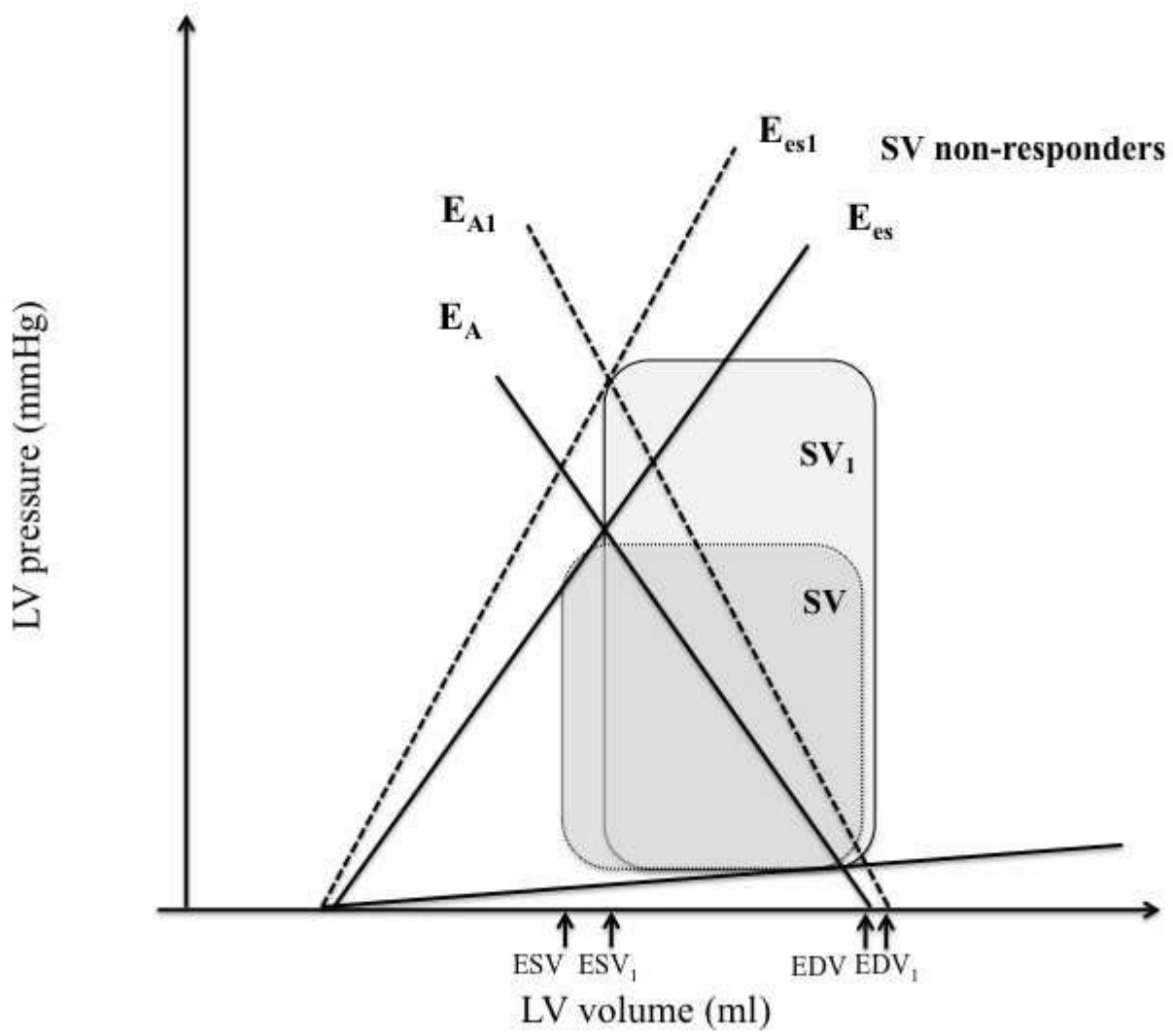
**Figure. 1:** Study flow chart

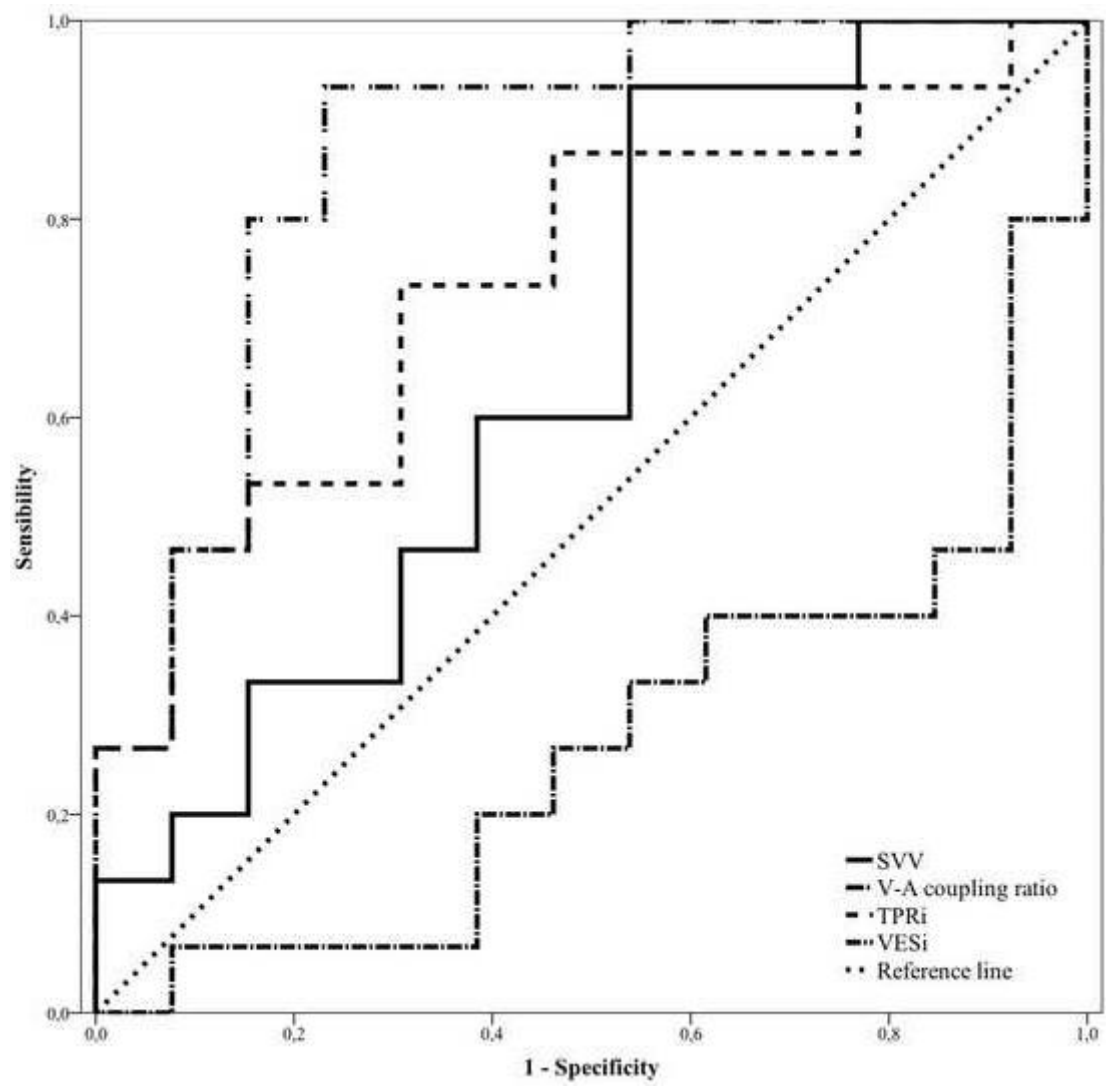
**Figure. 2:** Ventricular pressure-volume diagram in SV responder patients (A). Ventricular pressure-volume diagram in SV non-responder patients (B).

**Figure. 3:** Receiving operating curves (ROC) of  $E_A/E_{es}$ , SVV, TPRi, and SVi to discriminate response of SV to norepinephrine infusion.











**Table 1.** Characteristics of the study participants on inclusion. Values are expressed as the mean  $\pm$  SD or the number (%). **CABG**, coronary artery bypass graft. **SAPS 2**, new simplified acute physiology score ; **ScVO<sub>2</sub>**, central venous saturation. P value refers to comparison between SV responders and SV non-responders patients.

<b>Variables</b>	<b>SV responders (n=15)</b>	<b>SV non-reponders (n=13)</b>	<b>P value</b>
Age (mean $\pm$ SD, years)	69 $\pm$ 10	69 $\pm$ 9	NS
Gender (F/M)	4/11	3/10	NS
Body mass index (Kg m <sup>-2</sup> )	31.4 $\pm$ 6	30.3 $\pm$ 5	NS
SAPS 2, (mean $\pm$ SD)	48 $\pm$ 13	40 $\pm$ 13	NS
Disease, n (%)			
Arterial hypertension	13 (87)	10 (77)	NS
Aortic stenosis	7 (47)	7 (54)	NS
Diabetes mellitus	5 (33)	3 (23)	NS
Dyslipidaemia	5 (33)	7 (54)	NS
Heart surgery, n (%)			
Aortic valve replacement	9 (54)	9 (69)	
CABG	2 (13)	3 (23)	
Mixed (aortic valve replacement and CABG)	2 (13)	0	NS
Other (atrial myxoma, ascending aorta)	2 (13)	1 (8)	
<b>LVEF (% , mean<math>\pm</math> SD)</b>	<b>51 <math>\pm</math> 9</b>	<b>56 <math>\pm</math> 15</b>	<b>NS</b>
Cardiopulmonary bypass time (min, mean $\pm$ SD)	108 $\pm$ 49	98 $\pm$ 35	NS
ICU stays (days, median 25 <sup>le</sup> -75 <sup>le</sup> )	3 (2-6)	3 (2-5)	NS
Respiratory parameters			
Tidal volume (ml kg <sup>-1</sup> of predicted body weight, mean (SD),	7.7 $\pm$ 0.5	7.7 $\pm$ 0.7	NS
Total PEEP (cmH <sub>2</sub> O, mean $\pm$ SD)	6 $\pm$ 1	6 $\pm$ 2	NS

Propofol (mg.kg <sup>-1</sup> h <sup>-1</sup> , mean ±SD)	1.5 ± 0.5	1.6 ± 0.4	NS
Cumulated fluid infusion before norepinephrine treatment (ml, mean ± SD)	717 ± 297	827 ± 188	NS
Norepinephrine dose (µg.kg min <sup>-1</sup> , median (25 <sup>le</sup> -75 <sup>le</sup> ))	0.10 (0.064-0.2)	0.089 (0.069-0.11)	NS
ScVO <sub>2</sub> (% , mean ± SD)	59 ± 12	62 ± 7	NS
Arterial lactates (mmol l <sup>-1</sup> , mean ± SD)	1.62 ± 0.52	1.76 ± 0.66	NS
Death (n, %)	1 (7)	1 (8)	NS

**Table 2. Comparison of hemodynamic parameters in stroke volume responders and non-responders.** CI, cardiac index; CVP, central venous pressure; DAP, diastolic arterial pressure; ESV, left ventricular end systolic volume; EDV, left ventricular end diastolic volume; HR, heart rate; IVC, inferior vena cava; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NE, norepinephrine; PP, pulse pressure; SAP, systolic arterial pressure; SV<sub>i</sub>, indexed stroke volume; TPR<sub>i</sub>, indexed total peripheral resistance; SVV, respiratory variation of SV; PPV, respiratory variation of PP; *P*-value refers to comparison between SV responders and SV Non-responders. <sup>§</sup> (*p*<0.05) refers to comparison within groups, post versus pre-NE infusion.

Hemodynamic variables	SV Responders (n=15)	SV Non-responders (n=13)	<i>P</i> value
<b>SV<sub>i</sub> (ml.m<sup>-2</sup>, mean ± SD)</b>			
Pre-NE	19 ± 8	27 ± 10	0.038
Post-NE	25 ± 10 <sup>§</sup>	27 ± 8	NS
<b>ESV (ml, mean ± SD)</b>			
Pre-NE	94 ± 59	54 ± 16	0.027
Post-NE	86 ± 55	62 ± 15	NS
<b>EDV (ml, mean ± SD)</b>			
Pre-NE	133 ± 63	106 ± 33	NS
Post-NE	138 ± 57	114 ± 22	NS
<b>CI (ml.min<sup>-1</sup>.m<sup>-2</sup>, mean ± SD)</b>			
Pre-NE	1.56 ± 0.6	1.95 ± 0.5	0.033
Post-NE	1.99 ± 0.6 <sup>§</sup>	2.05 ± 0.5	NS
<b>HR (bpm, mean ± SD)</b>			
Pre-NE	81 ± 19	76 ± 16	NS
Post-NE	80 ± 19	79 ± 18	NS
<b>SAP (mmHg, mean ± SD)</b>			
Pre-NE	84 ± 11	85 ± 10	NS
Post-NE	119 ± 8 <sup>§</sup>	119 ± 13 <sup>§</sup>	NS
<b>DAP (mmHg, mean ± SD)</b>			
Pre-NE	46 ± 8	46 ± 8	NS
Post-NE	60 ± 9 <sup>§</sup>	61 ± 13 <sup>§</sup>	NS
<b>MAP (mmHg, mean ± SD)</b>			
Pre-NE	59 ± 11	59 ± 8	NS
Post-NE	80 ± 7 <sup>§</sup>	80 ± 11 <sup>§</sup>	NS
<b>PP (mmHg, mean ± SD)</b>			
Pre-NE	37 ± 10	39 ± 9	NS
Post-NE	58 ± 10 <sup>§</sup>	58 ± 12 <sup>§</sup>	NS
<b>CVP (mmHg, mean ± SD)</b>			
Pre-NE	7 ± 4	8 ± 4	NS
Post-NE	9 ± 4 <sup>§</sup>	10 ± 4 <sup>§</sup>	NS
<b>SVV (% , mean ± SD)</b>			
Pre-NE	25 ± 113	19 ± 10	NS
Post-NE	22 ± 9	23 ± 15	NS
<b>PPV (% , mean ± SD)</b>			
Pre-NE	15 ± 7	13 ± 7	NS
Post-NE	11 ± 6 <sup>§</sup>	11 ± 8	NS
<b>Ea<sub>dyn</sub> (units, median (25<sup>le</sup>-75<sup>le</sup>))</b>			
Pre-NE	0.7 (0.38-1)	0.78 (0.45-0.89)	NS
Post-NE	0.58 (0.3-0.79)	0.44 (0.27-1.26)	NS
<b>IVC diameter (cm, mean ± SD)</b>			
Pre-NE	1.69 ± 0.3	1.79 ± 0.3	NS
Post-NE	1.66 ± 0.7	1.64 ± 0.4	NS

<b>LVEF (% , mean <math>\pm</math> SD)</b>			
Pre-NE	37 $\pm$ 12	48 $\pm$ 11	0.011
Post-NE	44 $\pm$ 19 <sup>§</sup>	47 $\pm$ 11	NS
<b>Total arterial compliance (ml. mmHg<sup>-1</sup>, mean <math>\pm</math> SD)</b>			
Pre-NE	1.06 $\pm$ 0.44	1.4 $\pm$ 0.58	NS
Post-NE	0.88 $\pm$ 0.37 <sup>§</sup>	0.89 $\pm$ 0.24 <sup>§</sup>	NS
<b>TPRi (mmHg.ml<sup>-1</sup>.m<sup>-2</sup>, median (25<sup>le</sup>-75<sup>le</sup>))</b>			
Pre-NE	34 (28-51)	26 (23-36)	0.033
Post-NE	37 (30-57)	35 (30-45) <sup>§</sup>	NS
<b>Arterial elastance (E<sub>A</sub>) (mmHg.ml<sup>-1</sup>, median (25<sup>le</sup>-75<sup>le</sup>))</b>			
Pre-NE	1.8 (1.4-3.3)	1.6 (1.1-2)	NS
Post-NE	1.9 (1.6-3.3) <sup>§</sup>	2.1 (1.8-2.6) <sup>§</sup>	NS
<b>Ventricular elastance (E<sub>es</sub>) (mmHg.ml<sup>-1</sup>, median (25<sup>le</sup>-75<sup>le</sup>))</b>			
Pre-NE	0.83 (0.57-1.34)	1.15 (0.72-1.72)	NS
Post-NE	1.14 (0.84-1.56) <sup>§</sup>	1.58 (1.14-1.93) <sup>§</sup>	NS
<b>E<sub>A</sub>/E<sub>es</sub> ratio (median (25<sup>le</sup>-75<sup>le</sup>))</b>			
Pre-NE	2 (1.7-2.9)	1.34 (1.1-1.61)	0.0001
Post-NE	1.8 (1.4-2.4) <sup>§</sup>	1.36 (1.23-1.69)	0.029

### **c. L'élastance artérielle dynamique constitue un indice prédictif du besoin en noradrénaline dans le syndrome vasoplégique**

Les vasopresseurs, dont la noradrénaline, sont une partie essentielle de la gestion des patients avec une insuffisance circulatoire aiguë vasoplégique. Après prise en charge réanimatoire avec obtention des objectifs hémodynamiques, traitement de la cause du choc, la phase de sevrage constitue une étape importante et nécessaire à la sortie du patient de réanimation. Le but de cette phase est de sevrer le patient des médicaments vasoactifs sans altérer la perfusion tissulaire. Aucun auteur n'avait étudié la possibilité de variables hémodynamiques à prédire la dépendance de la pression artérielle à la noradrénaline. En pratique clinique, le sevrage de la noradrénaline est laissé à l'appréciation des équipes soignantes.

L'élastance artérielle dynamique avait été proposée comme un indicateur dynamique du tonus artériel (36-39). Plusieurs auteurs ont par la suite montré que cet indice pouvait être utilisé pour évaluer le tonus vasculaire, et que des valeurs élevées étaient associées à une décroissance des posologies de noradrénaline. L' $E_{a_{dyn}}$  peut donc constituer une approche fonctionnelle de l'évaluation du tonus artériel semblable aux indices dynamiques de précharge dépendance utilisés pour prédire une précharge dépendance (36, 37).

En l'absence de données, nous avons mis en place une étude évaluant la capacité de l' $E_{a_{dyn}}$  à prédire une baisse de la pression artérielle avec la baisse de la noradrénaline. Ce travail s'est intéressé à des patients de réanimation (intubés ventilés) en phase de sevrage de noradrénaline avec une posologie moyenne de noradrénaline de  $0,25 \text{ } \mu\text{g Kg}^{-1} \text{ min}^{-1}$ , et monitorés avec une analyse du contour de l'onde de pouls calibrée (système PICCO™). La diminution de noradrénaline était standardisée ( $0,01 \text{ } \mu\text{g Kg}^{-1} \text{ min}^{-1}$ ), et une seule étape de diminution était analysée. Comme attendu, l' $E_{a_{dyn}}$  prédisait la dépendance de la pression artérielle à la noradrénaline, et constituait la seule variable de la charge artérielle associée à cette dépendance. Ce travail a confirmé l' $E_{a_{dyn}}$  comme indice fonctionnel du tonus vasomoteur.

RESEARCH

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# Dynamic arterial elastance predicts mean arterial pressure decrease associated with decreasing norepinephrine dosage in septic shock

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## Abstract

**Introduction:** Gradual reduction of the dosage of norepinephrine (NE) in patients with septic shock is usually left to the physician's discretion. No hemodynamic indicator predictive of the possibility of decreasing the NE dosage is currently available at the bedside. The respiratory pulse pressure variation/respiratory stroke volume variation (dynamic arterial elastance ( $E_{a_{dyn}}$ )) ratio has been proposed as an indicator of vascular tone. The purpose of this study was to determine whether  $E_{a_{dyn}}$  can be used to predict the decrease in arterial pressure when decreasing the NE dosage in resuscitated sepsis patients.

**Methods:** A prospective study was carried out in a university hospital intensive care unit. All consecutive patients with septic shock monitored by PICCO<sub>2</sub> for whom the intensive care physician planned to decrease the NE dosage were enrolled. Measurements of hemodynamic and PICCO<sub>2</sub> variables were obtained before/after decreasing the NE dosage. Responders were defined by a >15% decrease in mean arterial pressure (MAP).

**Results:** In total, 35 patients were included. MAP decreased by >15% after decreasing the NE dosage in 37% of patients ( $n = 13$ ). Clinical characteristics appeared to be similar between responders and nonresponders.  $E_{a_{dyn}}$  was lower in responders than in nonresponders (0.75 (0.69 to 0.85) versus 1 (0.83 to 1.22),  $P < 0.05$ ). Baseline  $E_{a_{dyn}}$  was correlated with NE-induced MAP variations ( $r = 0.47$ ,  $P = 0.005$ ). An  $E_{a_{dyn}}$  less than 0.94 predicted a decrease in arterial pressure, with an area under the receiver-operating characteristic curve of 0.87 (95% confidence interval (95% CI): 0.72 to 0.96;  $P < 0.0001$ ), 100% sensitivity, and 68% specificity.

**Conclusions:** In sepsis patients treated with NE,  $E_{a_{dyn}}$  may predict the decrease in arterial pressure in response to NE dose reduction.  $E_{a_{dyn}}$  may constitute an easy-to-use functional approach to arterial-tone assessment, which may be helpful to identify patients likely to benefit from NE dose reduction.

## Introduction

Vasopressors are an essential part of the early management of patients with circulatory shock [1]. Treatment of circulatory shock must include correction of the cause of shock and hemodynamic stabilization, primarily by fluid infusion and administration of vasoactive agents [2,3]. Finally, after achieving a minimal acceptable arterial pressure, providing adequate oxygen availability, and treating the cause of shock, the dose-reduction phase is necessary before discharge of the patient from the ICU. The purpose of this phase of treatment is to wean

the patient from vasoactive agents and to promote spontaneous polyuria or induce fluid elimination to achieve a negative fluid balance [2]. The choice of appropriate treatment is based on a good understanding of the underlying pathophysiological mechanisms.

Norepinephrine (NE) is recommended in national and international guidelines as first-line hemodynamic support for septic shock [4]. In the SOAP study, norepinephrine was the vasopressor drug most commonly used (80% of cases), in combination with dobutamine in 30% of cases [5]. The use of NE is justified by its pharmacodynamic properties that induce arterial and venous vasoconstriction, allowing rapid correction of arterial pressure [6-8]. During the recovery phase of shock, as vasoplegia resolves after improvement of vasoreactivity, a theoretic risk of tissue

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hypoperfusion exists because of excessive vasoconstriction, especially when blood volume is not optimized. Decreasing the NE dosage is therefore an important step. However, few studies on the modalities of decreasing the NE dosage have been published [9]. The method used to decrease the NE dosage is often arbitrary and may unnecessarily prolong the potentially harmful use of this agent. No hemodynamic indicator predictive of the possibility of NE dose reduction is currently available at the bedside.

The  $\Delta\text{respPP}/\Delta\text{respSV}$  ratio has recently been proposed as a dynamic indicator of arterial tone (arterial dynamic elastance:  $E_{a_{\text{dyn}}}$ ) [10,11]. Several authors have subsequently shown that this indicator can be used to assess vascular tone at the bedside, and that higher values were associated with the de-escalation of NE dose with fluid expansion [12,13].  $E_{a_{\text{dyn}}}$  was also able to predict the hemodynamic response in mean arterial pressure (MAP) to fluid administration in hypotensive, preload-dependent patients [12].  $E_{a_{\text{dyn}}}$  can therefore constitute a functional approach to the assessment of arterial tone similar to preload responsiveness parameters that are used to predict the hemodynamic response to a change in cardiac preload [12-14].

The primary objective of this study was to answer the following question: can dynamic arterial elastance be used to predict the decrease in arterial pressure induced by decreasing the NE dosage in sepsis patients? We also describe the effect of decreasing the NE dosage in resuscitated septic shock patients.

## Materials and methods

### Ethics

This study was approved by the Institutional Review Board (IRB) for human subjects (Comité de Protection des Personnes Nord-Ouest II CHU, Place V. Pauchet, 80054 AMIENS Cedex 1). Informed consent was waived, as the IRB considered the protocol to be an observational study. In our institute, the dosage of NE is decreased by 3.3  $\mu\text{g}/\text{min}$  each hour for as long as MAP remains higher than 65 mm Hg. The indication to decrease the dosage of NE was left to the physician's discretion. Only a one-step NE dose reduction was assessed in this study.

### Patients

A prospective, observational study was conducted at Amiens University Hospital intensive care unit over a period of 12 months (2012). Inclusion criteria were all consecutive patients with a diagnosis of severe sepsis or septic shock, according to the criteria of the Surviving Sepsis Campaign, treated with NE, for whom the attending physician decided to decrease the NE dosage, and who were monitored with a PICCO monitoring device [4]. Exclusion criteria were patients treated with epinephrine and/or dobutamine, arrhythmia, intraabdominal hypertension, and patients younger than 18 years. All patients had

been sedated with continuous infusion of midazolam and sufentanil and were ventilated in volume-controlled mode.

### Hemodynamic parameters

An internal jugular vein central venous catheter was placed in all patients, and a thermistor-tipped arterial catheter (PV2024; Pulsion Medical Systems, Munich, Germany) in the femoral artery connected to a PICCO<sub>2</sub> monitoring device was used to measure cardiac output (CO). Estimation of stroke volume by pulse-contour analysis was calibrated by transpulmonary thermodilution with injection of three 15-ml boli of cold saline. The mean value of three consecutive measurements was used for analysis of stroke volume (SV), CO, global end-diastolic volume (GEDV), and cardiac function index (CFI). If the difference between the three values was greater than 10%, two additional measurements were subsequently performed. Respiratory variations of pulse pressure ( $\Delta\text{respPP}$ ) and stroke volume ( $\Delta\text{respSV}$ ) were monitored by using PICCO<sub>2</sub>. Each value was the average of five consecutive measurements. Central venous pressure (CVP) and blood pressure were measured with a transducer zeroed at the level of the midaxillary line.

### Study protocol

The following clinical parameters were recorded: age, gender, weight, surgical/medical history, main diagnosis, and IGS2. Heart rate (HR), systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), CVP,  $\Delta\text{respPP}$ ,  $\Delta\text{respSV}$ , CO, systemic vascular resistance (SVR), and GEDV were recorded at baseline, with the patient adapted to the ventilator. A passive leg raising (PLR) test was performed to evaluate the effects on pulse-contour analysis of CO [15]. The dose of NE was decreased 10 minutes after PLR. After stabilization of hemodynamic variables, as assessed by the absence of variation of MAP by >10% over a 30-minute period, a second set of measurements with thermodilution (SAP, MAP, DAP, HR, CVP, CO, SVR, GEDV,  $\Delta\text{respPP}$ ,  $\Delta\text{respSV}$ ) was recorded. Dynamic arterial elastance ( $E_{a_{\text{dyn}}}$ ) was defined as the ratio of  $\Delta\text{respPP}$  to  $\Delta\text{respSV}$ . Static arterial compliance (C) (ml/mm Hg) was calculated as the ratio of SV to pulse pressure [15].

Ventilator settings were maintained at constant levels throughout the study period. Thermodilution calibration was performed before and after decreasing the dose of NE.

### Statistical analysis

A sample of 30 patients would be sufficient to demonstrate that  $E_{a_{\text{dyn}}}$  can predict a decrease in arterial pressure in response to decreasing the NE dosage with an AUC greater than 0.80, a power of 80%, an alpha risk of 0.05, and a beta risk of 0.2. Thirty-five patients were therefore recruited by taking into account the exclusion criteria. The distribution

of the variables was assessed by using D'Agostino-Pearson test. Data are expressed as proportion (percentage), mean (standard deviation), or median (25<sup>th</sup> to 75<sup>th</sup> percentiles), as appropriate. Nonresponders and responders were defined by MAP variation (expressed as a percentage) after decreasing the dose of NE. A positive response was defined as a  $\geq 15\%$  decrease in MAP [11]. The nonparametric Wilcoxon rank sum test, Student paired t test, Student t test, and Mann-Whitney test were used to assess statistical significance, as appropriate. Linear correlations were tested with the Spearman rank method. A receiver-operating characteristic curve (ROC) was established for SVR, arterial compliance, and  $E_{a_{dyn}}$ . The test previously described by DeLong and colleagues was used to compare areas under the ROC curve (AUC) for each variable. Differences with a P value  $< 0.05$  were considered statistically significant. Medcalc 12.7.7.0 software (Mariakerke, Belgium) was used to perform statistical analysis.

**Results**

Thirty-five patients with septic shock monitored by PICCO2 were included. The most common cause of septic shock was pneumonia and peritonitis (Table 1). Patients were included on day 6 (range, days 3 to 17) of admission to ICU. Thirteen (37%) of the 35 patients in whom the NE dosage was decreased were classified as arterial pressure responders because their MAP decreased by more than 15%.

In pressure-responder patients, the dosage of NE was decreased from 0.25 (0.14 to 0.58) to 0.23 (0.1

to 0.54)  $\mu\text{g/kg/min}$  in pressure-nonresponder patients, the dosage of NE was decreased from 0.38 (0.12 to 1.2) to 0.34 (0.09 to 1.2)  $\mu\text{g/kg/min}$ . The median dose was not statistically different between the two groups ( $P = 0.43$ ). The dosage of norepinephrine was decreased by 3.3  $\mu\text{g/min}$  in all patients. At baseline, eight patients had  $\Delta\text{respPP}$  and/or  $\Delta\text{respSV} > 15\%$ . Apart from these patients, two were classified as pressure responders. Baseline CO variations in response to PLR were not significantly different between responders and nonresponders (1.6% (-4 to 8) versus 2.1% (-1 to 6),  $P = 0.87$ ). SV decreased by more than 15% after decreasing the norepinephrine dosage in two patients.

Baseline  $E_{a_{dyn}}$  was lower in patients in whom arterial pressure decreased after decreasing the dose of norepinephrine (Figure 1, Table 2). Arterial pressure and SVR decreased, and arterial compliance increased after decreasing the norepinephrine dosage in responders. SV, CO, EDGV,  $\Delta\text{respSV}$ ,  $\Delta\text{respPP}$ , and CFI did not vary significantly in response to decreasing the norepinephrine dosage.

$E_{a_{dyn}}$  was correlated with SAP, MAP, and DAP variations in response to decreasing the norepinephrine dosage ( $r = 0.41$ ;  $P = 0.015$ ;  $r = 0.47$   $P = 0.005$ ;  $r = 0.49$   $P = 0.003$ ), but no correlation was observed between SVR, SV variations, and a decreased dosage of NE ( $r = 0.004$ ,  $P = 0.982$ ;  $r = 0.26$ ,  $P = 0.14$ , respectively).  $E_{a_{dyn}}$  was not correlated with norepinephrine dose ( $r = 0.23$ ,  $P = 0.19$ ).

In the overall population,  $E_{a_{dyn}}$  predicted the decrease in arterial pressure with an AUC of 0.87 (95% CI, 0.72 to 0.96;  $P < 0.001$ ) (Figures 1 and 2). The best cut-off was 0.94. Table 3 reports the various cut-off values for  $E_{a_{dyn}}$ . Arterial compliance and SVR were not predictive, with an AUC of 0.61 (95% CI, 0.43 to 0.77;  $P = 0.32$ ) and 0.54 (95% CI, 0.36 to 0.71;  $P = 0.41$ ), respectively.

**Discussion**

This study, conducted on resuscitated sepsis patients, demonstrated that (a)  $E_{a_{dyn}}$  may be a functional indicator of arterial tone when decreasing the dose of NE that can differentiate patients in whom MAP is maintained from those in whom MAP decreases in response to a fixed dose reduction. An  $E_{a_{dyn}}$  less than 0.94 predicted a 15% decrease in MAP in response to decreasing the dose of NE. (b) The arterial pressure change associated with decreasing the dose of NE may be mostly due to the arterial vasoconstrictor ( $\alpha$ -adrenergic) effect of NE.

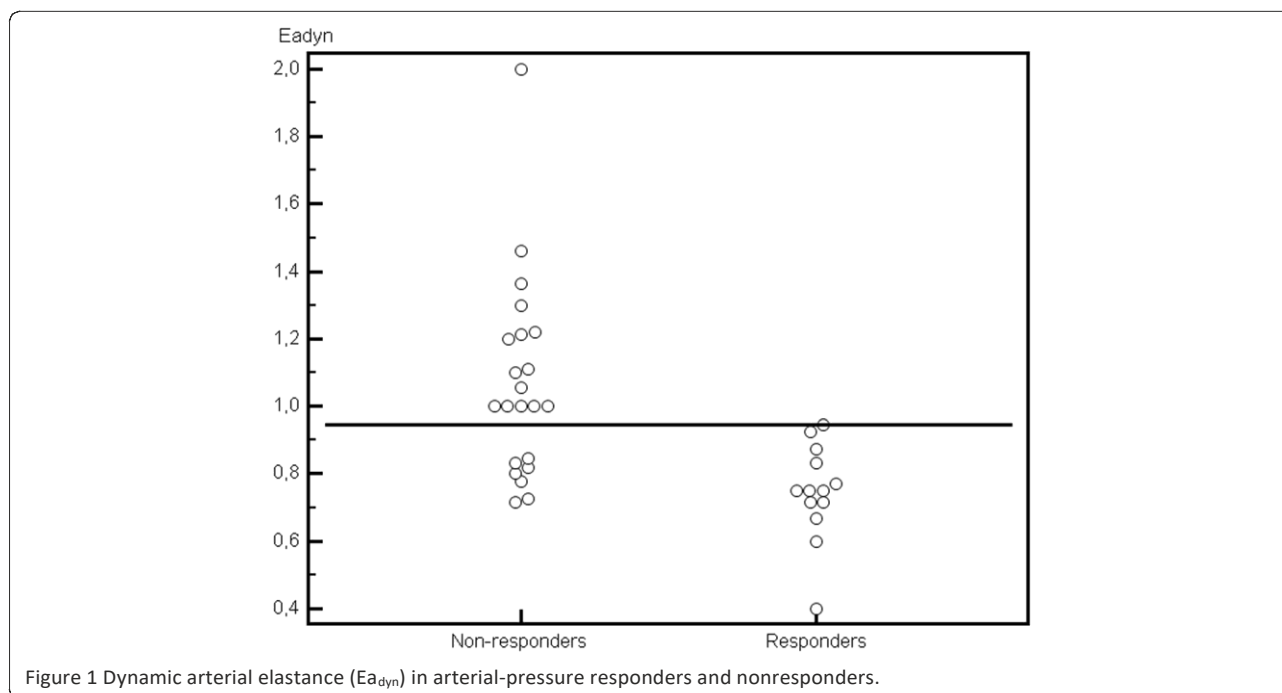
No study has previously evaluated the predictive value of an indicator for NE dose reduction in septic shock patients.  $E_{a_{dyn}}$  has recently been proposed as a marker of arterial tone or, more specifically, a marker of arterial stiffness [14]. In postoperative cardiac surgery patients, vasodilator therapy decreased  $E_{a_{dyn}}$ , whereas norepinephrine infusion increased this indicator [16]. In ICU patients, an  $E_{a_{dyn}}$  less than 0.9 was predictive of persistent arterial

**Table 1** Main patient characteristics on inclusion

Age (mean (SD), years)	65 (16)
Gender (F/M)	13/22
SAPS 2 (mean (SD))	52 (12)
Etiology of shock, n (%)	
Pneumonia	15 (42)
Peritonitis	12 (34)
Endocarditis	3 (9)
Cholangitis	2 (6)
Salpingitis	1 (3)
<i>Clostridium</i> infection	1 (3)
Bloodstream infection	1 (3)
Respiratory parameters	
Tidal volume ((mean (SD), ml/kg of predicted body weight)	7.7(1.1)
Respiratory rate (mean (SD), per minute)	21 (4)
Plateau pressure ((mean (SD), cmH <sub>2</sub> O)	23 (6)
Total PEEP ((mean (SD), cmH <sub>2</sub> O)	7 (4)
Left ventricular ejection fraction (%)	55 (9)

Values are expressed as mean ( $\pm$  standard deviation) or number (%). BMI, body mass index; SAPS 2, Simplified Acute Physiology Score 2.





hypotension after fluid challenge, despite an increase in CO. [12]. In surgical patients,  $E_{a_{dyn}}$  was found to discriminate successfully responders and nonresponders to dose de-escalation with volume expansion [13].

In the present study, we demonstrated that  $E_{a_{dyn}}$  can identify patients in whom arterial pressure will decrease in response to NE dose reduction. Moreover, only  $E_{a_{dyn}}$  was predictive of the decrease in arterial pressure with a cut-off value close to previously published values [12,13].

Arterial pulse pressure results from the interaction between the blood volume ejected from the ventricle and the arterial system, which comprises several phenomena: stroke volume (SV), arterial wave reflection, wall stiffness, total peripheral resistance. The relation between arterial pressure and arterial volume is curvilinear [17]. In this context,  $E_{a_{dyn}}$  may indicate in which part of the curve the patient is situated.  $E_{a_{dyn}}$  may constitute a functional approach to arterial tone assessment in the same way as preload responsiveness indices that are used to predict fluid responsiveness to a change in cardiac preload [12,14].  $E_{a_{dyn}}$  was lower in pressure responders, suggesting that SV variations induced low variations in PP due to the lower central vasomotor tone. Decreasing the NE dosage induced increased arterial compliance, which was even more marked in pressure responders. As discussed later, NE dose reduction induced only arterial  $\alpha$ -adrenergic effects with no change in cardiac preload and CO. These effects may have been less marked than those observed in previous studies because of the limited decrease of the NE dose [8,18], but the effects were sufficient to alter vascular tone and the relation between PP and SV as assessed by

arterial compliance, particularly in pressure-responder patients with a low  $E_{a_{dyn}}$ . Because SV did not vary significantly, the decrease in arterial pressure (MAP and PP) was associated with changes in SVR and arterial compliance after the decrease of the norepinephrine dosage.

SVR was not significantly different between the two groups of patients and did not predict the subsequent course of arterial pressure. These results may be because SVR reflects a pressure difference between MAP and CVP, whereas, from a physiological point of view, the cardiovascular system comprises two pressure systems with a waterfall phenomenon [19]. SVR therefore does not reflect vascular tone, although it can be considered to be a component of vascular tone. At baseline, arterial compliance was probably not significantly different because of our small sample size, but appeared to be higher in pressure responders with low central vascular tone.

In the present study, the vascular effects of NE may depend on the sepsis patient's underlying cardiovascular state. The vascular response observed differed from that reported in previous published studies [8,18,20]. Several explanations can be proposed for these differences.

First, the patient's cardiovascular status at the time of measurement: In contrast with other studies, we studied patients in whom NE dose reduction was initiated by the attending physician. In previous studies, preload indices were lower and CO variations with PLR were higher than in our study, suggesting that patients were insufficiently fluid-loaded [8,18,20]. Moreover, most of the patients included in our study also had  $\Delta\text{respPP}$  values below the conventional cut-off for preload responsiveness:

Table 2 Cardiovascular variables in pressure responders and pressure nonresponders, expressed as median (25th to 75th percentiles) or mean (SD)

	Before	After
HR (beats/min)		
Responders	84 (15) <sup>a</sup>	83 (15) <sup>a</sup>
Nonresponders	95 (17)	95 (18)
SAP (mm Hg)		
Responders	119 (12)	94 (11) <sup>a, b</sup>
Nonresponders	119 (13)	116 (14) <sup>b</sup>
DAP (mm Hg)		
Responders	56 (4)	45 (5) <sup>a, b</sup>
Nonresponders	59 (13)	57 (13) <sup>b</sup>
PP (mm Hg)		
Responders	63 (10)	50 (8) <sup>a, b</sup>
Nonresponders	60 (12)	58 (11)
MAP (mm Hg)		
Responders	77 (6)	61 (6) <sup>a, b</sup>
Nonresponders	79 (12)	77 (12) <sup>b</sup>
CVP (mm Hg)		
Responders	11 (5)	11 (5)
Nonresponders	11 (5)	11 (5)
ΔrespSV (%)		
Responders	8 (6–15)	10 (8–15)
Nonresponders	10 (7–13)	10 (7–15)
ΔrespPP (%)		
Responders	7 (4–11)	9 (5–12)
Nonresponders	10 (8–14)	10 (5–15)
Ea <sub>dyn</sub>		
Responders	0.75 (0.69-0.85) <sup>a</sup>	0.79 (0.67-1.04)
Nonresponders	1 (0.83-1.22)	0.9 (0.74-1.07) <sup>b</sup>
Arterial compliance (ml/mm Hg)		
Responders	1.2 (0.93-1.5)	1.5 (1.2-1.8) <sup>a, b</sup>
Nonresponders	0.98 (0.86-1.3)	1.1 (0.9-1.3)
SV (ml)		
Responders	70 (58–101)	67 (57–95)
Nonresponders	60 (53–75)	63 (53–77)
CO (L/min)		
Responders	6.2 (1.3)	6 (1.4)
Nonresponders	6.1 (1.8)	6.05 (1.8)
GEDV (ml)		
Responders	1,367 (361)	1,313 (334)
Nonresponders	1,371 (329)	1,375 (350)
SVR (Dyn/s/cm <sup>-3</sup> )		
Responders	891 (222)	703 (194) <sup>a, b</sup>
Nonresponders	963 (377)	942 (359)

Table 2 Cardiovascular variables in pressure responders and pressure nonresponders, expressed as median (25th to 75th percentiles) or mean (SD) (Continued)

CFI (L/min)		
Responders	4.7 (1.1)	4.7 (1.1)
Nonresponders	4.6 (1.4)	4.5 (1.3)

CO, cardiac output; CFI, cardiac function index; ΔrespSV, respiratory Stroke Volume variation; ΔrespPP, respiratory pulse pressure variation; DAP, diastolic arterial pressure; Ea: arterial elastance; Ea<sub>dyn</sub>: dynamic arterial elastance; GEDV, global end-diastolic volume; HR, heart rate; MAP, mean arterial pressure; PLR, passive leg raising; PP, pulse pressure; SAP, systolic arterial pressure; SV, stroke volume. <sup>a</sup>P < 0.05 between groups, <sup>b</sup>P < 0.05 within groups.

eight patients had ΔrespPP over 15%. Among these patients, only two were classified as MAP responders and none significantly decreased their SV or increased their ΔrespPP and ΔrespSV values with NE decrease.

Another explanation could be that the dose of NE was not sufficiently decreased to induce any effects on venous return and cardiac preload [18,20]. The dosage of NE was decreased by a fixed dose that was lower than that used in studies evaluating effect of NE in sepsis patients. As multi-step NE dose reduction was not assessed in this study, we cannot exclude the possibility that these effects may be observed with more marked NE dose reduction. Decreasing the NE dosage resulted in a fall in arterial pressure with no significant change in cardiac preload and CO because patients were probably sufficiently fluid loaded (late phase of resuscitation). We observed an isolated decrease in arterial pressure with no decrease in CO, suggesting arterial α-adrenergic effects [8,16,17]. CFI, a surrogate marker of left ventricular function, did not decrease, suggesting no change in this index, whereas the decrease in arterial pressure was not related to α-receptors [21].

Our results must be interpreted cautiously, as up to 18% of patients had a false-positive response: despite a low Ea<sub>dyn</sub>, arterial pressure did not decrease by more than 15%. These results are in accordance with those reported by Hadian and colleagues [16], who observed that, in some patients, Ea<sub>dyn</sub> was not correlated with changing doses of vasoactive drugs. Nevertheless, Ea<sub>dyn</sub> had a high negative predictive value, showing that the upper Ea<sub>dyn</sub> cut-off value of 0.94 is highly predictive of successful NE dose reduction.

Another explanation could be that the dosage of NE was not decreased sufficiently in these patients to induce any significant vascular effects. This indicator was not sufficiently specific to contraindicate NE dose reduction by physicians/nurses at the bedside.

Further prospective interventional studies using algorithms with Ea<sub>dyn</sub> are needed to confirm the performance of this bedside indicator to adjust the NE dosage. Our sample size was small but the study was constructed to demonstrate the ability of Ea<sub>dyn</sub> to predict changes of

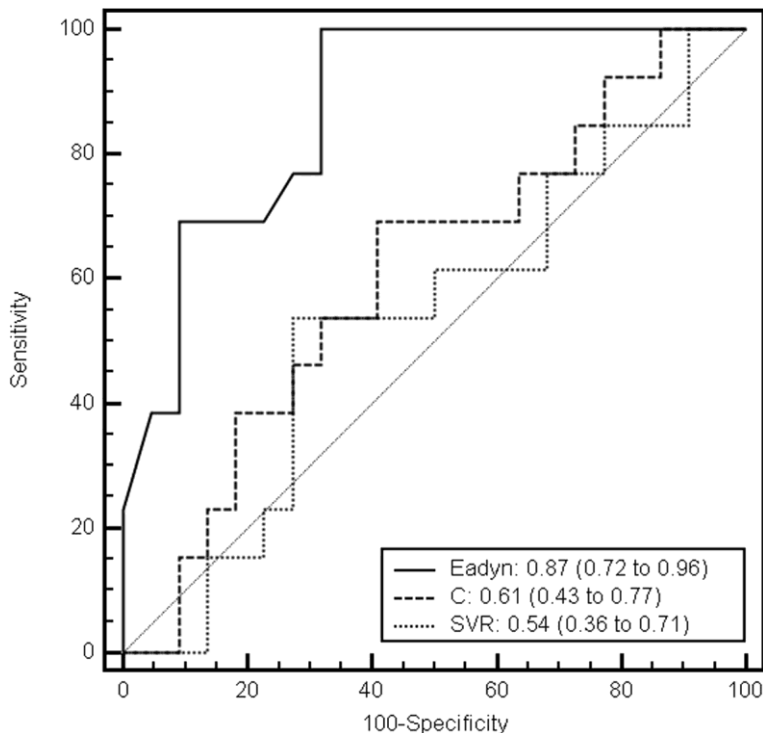


Figure 2 Receiver operating characteristic curves to discriminate decrease in arterial pressure with decreasing doses of norepinephrine.  $E_{a_{dyn}}$ , dynamic arterial elastance; C, arterial compliance; SVR, systemic vascular resistance.

MAP associated with decreasing the NE dosage. Some of the differences observed for hemodynamic parameters might have reached statistical significance with a larger patient cohort, although the directional changes would unlikely be reversed. We studied a one-step NE dose reduction that was the same for the overall population. As no further decrease in the NE dosage was evaluated, we cannot draw any conclusions concerning the subsequent course of hemodynamic parameters and  $E_{a_{dyn}}$  in response to a more marked reduction of the NE dose. We studied MAP changes only due to changes in NE doses and not due to other therapeutic interventions (for example, dobutamine weaning). These results cannot be extrapolated to patients concomitantly treated with dobutamine, who may represent up to 30% of all sepsis patients.

Another limitation could be mechanical ventilation that alters the predictability of volume-responsiveness indices. The influence of tidal volume on  $E_{a_{dyn}}$  was

probably marginal, as ventilatory parameters were kept constant during the study period. This relation remains constant and predictive, even during spontaneous ventilation, provided that  $\Delta respPP$  and  $\Delta respSV$  values are sufficiently large to define a slope [14,22]. Thermodilution was used as the reference method for CO measurement, but different CO results might have been obtained if another reference method had been used [23].

We used the PiCCO™ that does not report individual SV values on a beat-to-beat basis.  $\Delta respSV$  and  $\Delta respPP$  represent an average over 30 seconds. CO was calculated by using an algorithm based on the ventriculo-arterial coupling transfer function with thermodilution calibration for CO measurement. As a thermodilution calibration was performed before/after changing the NE dosage, we can assume that  $\Delta respSV$  was calibrated to the change of vascular tone induced by NE.

Table 3 Accuracy of  $\Delta respPP/\Delta respSV$  ratio (dynamic arterial elastance) to predict decrease in arterial pressure

Cut-off value (%)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value (%)	Negative predictive value (%)
0.94	100 (75–100)	68 (45–86)	3.14 (1.7–5.8)	0	65 (41–85)	100 (78–100)
0.83	77 (46–95)	73 (50–89)	2.82 (1.3–5.9)	0.32 (0.1–0.9)	63 (35–85)	84 (60–97)
0.77	69 (39–91)	86 (65–97)	5.08 (1.7–15.4)	0.36 (0.2–0.8)	75 (43–95)	83 (61–95)
0.7	23 (5–54)	100 (85–100)		0.77 (0.6–1)	100 (29–100)	69 (50–84)

## Conclusions

In this study, an  $Ea_{dyn}$  less than 0.94 was predictive of a decrease of arterial pressure in response to a decrease of the norepinephrine dosage in resuscitated sepsis patients. In contrast, no other hemodynamic variables were found to be predictive of a decrease in arterial pressure.  $Ea_{dyn}$  may constitute an easy-to-use functional approach to arterial tone assessment and may be helpful to identify patients likely to benefit from NE dose reduction. The high negative predictive value of this indicator can identify patients with a minimal risk of decreased arterial pressure. Further studies using algorithms with  $Ea_{dyn}$  are necessary to confirm the value and effectiveness of such an indicator at the bedside to adjust the NE dosage.

## Key messages

- Dynamic arterial elastance can be used to predict a decrease of arterial pressure associated with decreasing the norepinephrine a-dosage in sepsis patients.
- Systemic vascular resistance cannot predict the decrease of arterial pressure associated with decreasing the norepinephrine dosage in sepsis patients.
- The arterial pressure decrease associated with decreasing the norepinephrine dosage may be mostly due to the arterial vasoconstrictor effect of norepinephrine.

## Abbreviations

$\Delta respPP$ : Respiratory pulse pressure variation;  $\Delta respSV$ : respiratory stroke volume variation; CFI: cardiac function index; CO: cardiac output; CVP: central venous pressure; DAP: diastolic arterial pressure; Ea: arterial elastance;  $Ea_{dyn}$ : dynamic arterial elastance; GEDV: global end-diastolic volume; HR: heart rate; ICU: intensive care unit; MAP: mean arterial pressure; NE: norepinephrine; PLR: passive leg raising; PP: pulse pressure; SAP: systolic arterial pressure; SAPS 2: Simplified Acute Physiology Score 2; SV: stroke volume; SVR: systemic vascular resistance.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

PGG; Data acquisition: PGG, EB, ML; Analysis and interpretation: PGG, EL, HD; Drafting of the manuscript for important intellectual content: PGG, EL. All authors read and approved the manuscript.

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**d. L'utilisation de l'élastance artérielle dynamique dans un algorithme décisionnel diminue la durée de traitement par noradrénaline**

Suite aux travaux précédents sur la prédictibilité de l' $E_{a_{dyn}}$ , l'objectif suivant était de valider cet indice dans un algorithme décisionnel de prise en charge hémodynamique du traitement par noradrénaline (89). La littérature médicale est plus qu'abondante sur la mise en route de traitements salvateurs mais très peu détaillée sur l'arrêt des thérapeutiques lors de la récupération. L'auteur de cette thèse a donc mis en place une étude randomisée prospective dont l'objectif était de démontrer la supériorité d'un algorithme hémodynamique décisionnel basé sur la mesure de l' $E_{a_{dyn}}$  à une prise en charge habituelle. Il s'agit d'une étude de validation clinique de l'utilité de l' $E_{a_{dyn}}$  qui a prospectivement inclus 130 patients de chirurgie cardiaque traités par noradrénaline. Les résultats attendus furent démontrés avec une diminution par deux de la durée de traitement par noradrénaline et une diminution de la durée de séjour en réanimation. De manière intéressante, les patients n'étaient pas exposés à une augmentation du remplissage vasculaire et des altérations de la perfusion tissulaire. Au contraire, il y avait une tendance à une meilleure saturation veineuse centrale en oxygène. Ce travail permet de valider l'utilité et l'applicabilité clinique de l' $E_{a_{dyn}}$ .



# Monitoring dynamic arterial elastance as a means of decreasing the duration of norepinephrine treatment in vasoplegic syndrome following cardiac surgery: a prospective, randomized trial

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## Abstract

**Purpose:** To evaluate the ability of an algorithm based on dynamic arterial elastance to decrease the duration of norepinephrine treatment.

**Methods:** We performed a prospective, open-label, randomized study in patients requiring norepinephrine for vasoplegic syndrome after cardiac surgery with cardiopulmonary bypass. Patients were randomized to an algorithm-based intervention group or a control group. The primary outcome was the duration of norepinephrine treatment. The secondary outcomes included the total dose of norepinephrine, the length of stay (LOS) in the ICU, central venous oxygen saturation, arterial lactate levels, arrhythmia and diuresis.

**Results:** Of 130 included patients, 118 were analysed on an intention-to-treat basis (intervention group:  $n = 59$ ; control group:  $n = 59$ ). On inclusion, the intervention and control groups did not differ significantly in terms of demographic characteristics, surgical data or the prior duration of norepinephrine treatment [5 h (4–10) vs. 5 h (5–7), respectively;  $P = 0.543$ ]. The cumulative duration of norepinephrine treatment after inclusion was shorter in the intervention group than in the control group [17 h (13–26)] vs. 39 h (19–58), respectively; ( $P < 0.001$ ). The cumulative dose of norepinephrine and the LOS in the ICU were also lower in the intervention group ( $P < 0.05$ ). There were no intergroup differences for other outcomes (the sepsis-related organ failure score, central venous oxygen saturation, arrhythmia, and arterial lactate levels).

**Conclusion:** A haemodynamic algorithm based on dynamic arterial elastance was associated with a shorter duration of norepinephrine treatment and a shorter LOS in the ICU. Use of the algorithm did not alter perfusion parameters or increase the volume of fluid infused.

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**Take-home message:** In cardiac surgery patients suffering from vasoplegic syndrome, the use of an algorithm based on dynamic arterial elastance was associated with a shorter duration of norepinephrine treatment and a shorter LOS in the ICU. This difference did not alter perfusion parameters or fluid requirements.

## Introduction

Vasoplegic syndrome is a haemodynamic condition characterized by arterial hypotension and abnormally low systemic vascular resistance, whereas the cardiac output (CO) is unaffected or even abnormally high [1, 2]. The syndrome has been observed in various clinical settings (including sepsis, anaphylaxis, and the aftermath of



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**Keywords:** Vasoplegic syndrome, Dynamic arterial elastance, Norepinephrine

cardiac surgery) and affects up to 30% of patients being operated on in cardiac surgery departments [2]. Treatment of vasoplegic syndrome is based on the intravenous infusion of a vasopressor (usually norepinephrine) [3, 4]. During the recovery phase, weaning the patient off norepinephrine is an important step during which a lack of preload (i.e. hypovolaemia) may affect tissue hypoperfusion. Thus, optimization of norepinephrine treatment and appropriate haemodynamic management are important issues [5, 6]. Pinsky suggested that the  $\Delta\text{respPP}/\Delta\text{respSV}$  ratio is a functional index of arterial tone (arterial dynamic elastance,  $E_{a\text{dyn}}$ ) [7]. Several researchers subsequently demonstrated that  $E_{a\text{dyn}}$  is able to predict the arterial pressure response to fluid expansion—even in spontaneously breathing patients [8–12]. Furthermore,  $E_{a\text{dyn}}$  can predict a fall in blood pressure upon norepinephrine weaning in septic patients [13]. Vasodilator therapy decreases  $E_{a\text{dyn}}$ , whereas vasoconstrictor infusion increases this indicator [14, 15].

The ability of a haemodynamic algorithm based on  $E_{a\text{dyn}}$  to decrease the duration of norepinephrine treatment has not previously been evaluated. The main objective of the present study was to evaluate this potential ability in patients suffering from vasoplegic syndrome after cardiac surgery. We also evaluated the  $E_{a\text{dyn}}$ -based algorithm's impact on tissue perfusion, fluid expansion, diuresis and length of stay (LOS) in the ICU.

## Materials and methods

### Patients

We performed a prospective, open-label, randomized, controlled, parallel-arm, single-centre clinical trial in a tertiary university hospital (Amiens, France) between October 2014 and August 2016. The trial was designed to investigate the potential superiority of a new haemodynamic treatment algorithm in patients treated with norepinephrine. After approval by the local independent ethics committee (CPP Nord Ouest II, Amiens, France; ref. 2014-002707-22, ClinicalTrials.gov Identifier: NCT02479529), patients were prospectively recruited by our clinical service and then randomized 2:2 into an intervention group or a control group by using online software (Clinsight™, Ennov group, Paris, France). Block randomization was performed (38 blocks of 4 patients). The patients or their proxies gave their written, informed consent to participation in the study.

The main inclusion criteria were as follows: age 18 years or over, cardiac surgery with the use of cardiopulmonary

bypass [coronary artery bypass grafting (CABG) or the surgical correction of valvular disease, combined surgery (CABG and valve disease) or surgery of the ascending aorta], and norepinephrine treatment in the ICU for an indication of vasoplegic syndrome following cardiac surgery; and a mean arterial pressure (MAP) over 70 mmHg. Vasoplegic syndrome was defined as persistent arterial hypotension (i.e. a MAP below 65 mmHg) despite fluid resuscitation, and the need for norepinephrine infusion to maintain or restore a MAP over 70 mmHg for more than 4 h [1, 2]. The main non-inclusion criteria were permanent arrhythmia (atrial fibrillation or frequent ectopic beats), treatment with dobutamine or epinephrine, pregnancy, legal guardianship or incarceration, a functional implanted cardiac pacemaker, hypothermia, refusal to participate, right heart failure, haemorrhagic shock and age under 18 years. The exclusion criteria were death of the patient, the occurrence of a serious adverse event preventing the study from continuing, the introduction of dobutamine or epinephrine, and withdrawal of consent.

### Haemodynamic management

The patients' electrocardiogram, pulse oxygen saturation and central venous blood pressure were continuously monitored. All patients underwent several transthoracic echocardiography examinations per day. The scheduled blood tests included arterial/venous blood gas measurements on admission to the ICU admission, 6 h thereafter and then several times a day on request by the attending physician. The decision to wean a patient off norepinephrine was taken by the attending physician and the resuscitation nurse on duty.

When patients displayed a MAP over 70 mmHg and received more than 4 h of norepinephrine treatment, they were included in the study and randomized. Next, the haemodynamic monitoring device was implanted. The type of haemodynamic monitoring depended on the study group. The control group was monitored with either invasive pulmonary arterial thermodilution (Vigilance 2®, Edwards Lifesciences, Irvine, USA) or continuous contour analysis of the pulse wave plus transpulmonary thermodilution (using the EV1000 Monitor, Edwards Lifesciences, Irvine, USA). In the intervention group, a femoral arterial catheter thermodilution system (PV2024, PULSION Medical Systems, Munich, Germany) was connected to a PICCO® or Pulsioflex® device (PULSION Medical Systems). Transpulmonary calibration (three 15-ml boluses of

cold physiological saline, or 20-ml boluses if the patient weighed over 100 kg) was performed every 4 h or after three successive changes in the norepinephrine dose level. The  $E_{\text{dyn}}$  was defined as the ratio between  $\Delta\text{respPP}$  and  $\Delta\text{respSV}$  [12], and was the mean average of three successive values over a 2-min period.

In the control group, patients were weaned off norepinephrine [electronic supplementary material (ESM 1)] with a stepwise decrease of  $0.01 \mu\text{g}^{-1} \text{kg}^{-1} \text{min}^{-1}$  every 15 min until the MAP remained above 70 mmHg. The decrease was interrupted whenever the MAP fell below 70 mmHg, and the preload was evaluated. In cases of preload dependency, volume expansion was performed by infusing 250 ml of either crystalloid solution [Ringer's lactate (Baxter, Guyancourt, France) or physiological saline solution (B-Braun Medical, Boulogne-Billancourt, France)] or colloid solution (Gelofusine<sup>®</sup> 4%, B-Braun Medical). The attending physicians was free to choose the type of volume expansion solution. In the absence of preload dependency, norepinephrine was increased at the previous step.

In the intervention group, norepinephrine weaning was performed as follows (ESM 2), with a stepwise decrease of  $0.01 \mu\text{g}^{-1} \text{kg}^{-1} \text{min}^{-1}$  every 15 min until  $E_{\text{dyn}}$  was over 0.94. The decrease was stopped if  $E_{\text{dyn}}$  fell below 0.94. If the MAP was below 70 mmHg and  $E_{\text{dyn}}$  was above 0.94, volume expansion was performed by infusing 250 ml of crystalloid solution [Ringer's lactate (Baxter, Guyancourt, France) or physiological saline solution (B-Braun Medical, Boulogne-Billancourt, France)] or colloid solution (Gelofusine<sup>®</sup> 4%). Again, the attending physician was free to choose the type of volume expansion solution.

Preload dependency was assessed with dynamic indices when applicable, by measuring SV variations during passive leg raising, and/or via fluid challenge.  $E_{\text{dyn}}$  was never used as an indicator of preload dependency.

All data were continuously recorded using Clinisoft<sup>™</sup> software (GE Healthcare, Little Chalfont, England) and then on an electronic case report form using Clinsight<sup>™</sup> software (Ennov group) by a physician (SB) who was not involved in the care of patients included in the study. The Clinisoft<sup>™</sup> software calculated the cumulative dose of norepinephrine. The following variables were recorded: age, gender, body weight, height, personal medical history, ASA score, logistic EuroSCORE, type of cardiac surgery, the preoperative left ventricular ejection fraction, the duration of cardiopulmonary bypass, the duration of aortic clamping, the need for intraoperative blood transfusion, extubation time, any occurrence of arrhythmia during the study and/or during the stay in the ICU, the LOS in the ICU and the overall LOS in the hospital. The following clinical and haemodynamic variables were recorded at several time points (at the beginning of

norepinephrine administration, on inclusion, 12 h after inclusion and every 24 h until the end of the norepinephrine infusion); the sepsis-related organ failure assessment (SOFA) score, heart rate, systolic blood pressure, diastolic blood pressure, MAP, central venous pressure, cardiac index, arterial lactate level, urine output (ml), central venous oxygen saturation ( $\text{ScvO}_2$ ), transfusions of packed red blood cells, platelets or fresh frozen plasma, cumulative volume of crystalloid solution, cumulative volume of colloid solution and cumulative dose of norepinephrine.

The following parameters were calculated: cumulative fluid intake (cumulative crystalloid + cumulative colloid volumes)/weight (kg)/duration (h) of norepinephrine treatment (expressed in  $\text{ml kg}^{-1} \text{h}^{-1}$ ) and cumulative diuresis (expressed in  $\text{ml kg}^{-1} \text{h}^{-1}$ ).

#### Statistical analysis

The primary endpoint for the duration of norepinephrine treatment was defined as the time interval between the initial infusion of norepinephrine and its withdrawal. The secondary endpoints were as follows: the cumulative dose of norepinephrine, diuresis (ml) during the study period, total fluid infused (ml) during the study period, arterial lactate levels,  $\text{ScvO}_2$ , the incidence of arrhythmia (atrial fibrillation, ventricular tachycardia or ventricular fibrillation) during the study period, deaths and LOS in the ICU.

According to Noether's nonparametric approach, inclusion of 116 patients (58 per group) would be required to show that the probability whereby norepinephrine treatment lasts longer in the control group than in the intervention group is 0.65. In other words, there would be a 65% chance that the duration of norepinephrine treatment in the control group is greater than that in the intervention group. Using the normal approximation to the reference, a probability of 0.65 corresponds to a standardized effect size of 0.54. With a power of 80%, a two-sided first-order error of 5% and a loss-to-follow-up rate of 10%, the required sample size was calculated to be 130 (i.e. 65 per group).

The normality of the data distribution was assessed using the Shapiro–Wilk test. Data are expressed as the mean  $\pm$  standard deviation or the median (25th to 75th percentiles), as appropriate. For intergroup comparisons of continuous variables, Student's paired *t* test was used if the data were distributed normally; otherwise, the Mann–Whitney rank sum test was used. The Chi squared test or Fisher's exact test was applied to categorical variables, as appropriate. The threshold for statistical significance was set to  $P < 0.05$  for primary endpoints. Given that we performed three repeated measures for the analysis reported in Table 3, a Bonferonni post hoc correction was applied; the threshold for statistical significance



was set to  $P < 0.0167$  ( $0.05/3$ ). A statistician performed the statistical analysis using R software (<https://www.r-project.org/>).

**Results**

Of the 1763 patients admitted to the ICU during the study period, 130 were randomized into the study (Fig. 1), and 118 were analysed on an intention-to-treat basis. One patient in the intervention group patient

presented with an arteriovenous fistula (treated with an endovascular technique) following the implementation of a Pulsioath<sup>®</sup> arterial catheter. The postoperative course was uneventful and the patient survived.

The intervention and control groups did not differ significantly with regard to their demographic characteristics (Table 1). One patient in the intervention group and two in the control group were not extubated. The median time to extubation (in hours) did not differ when

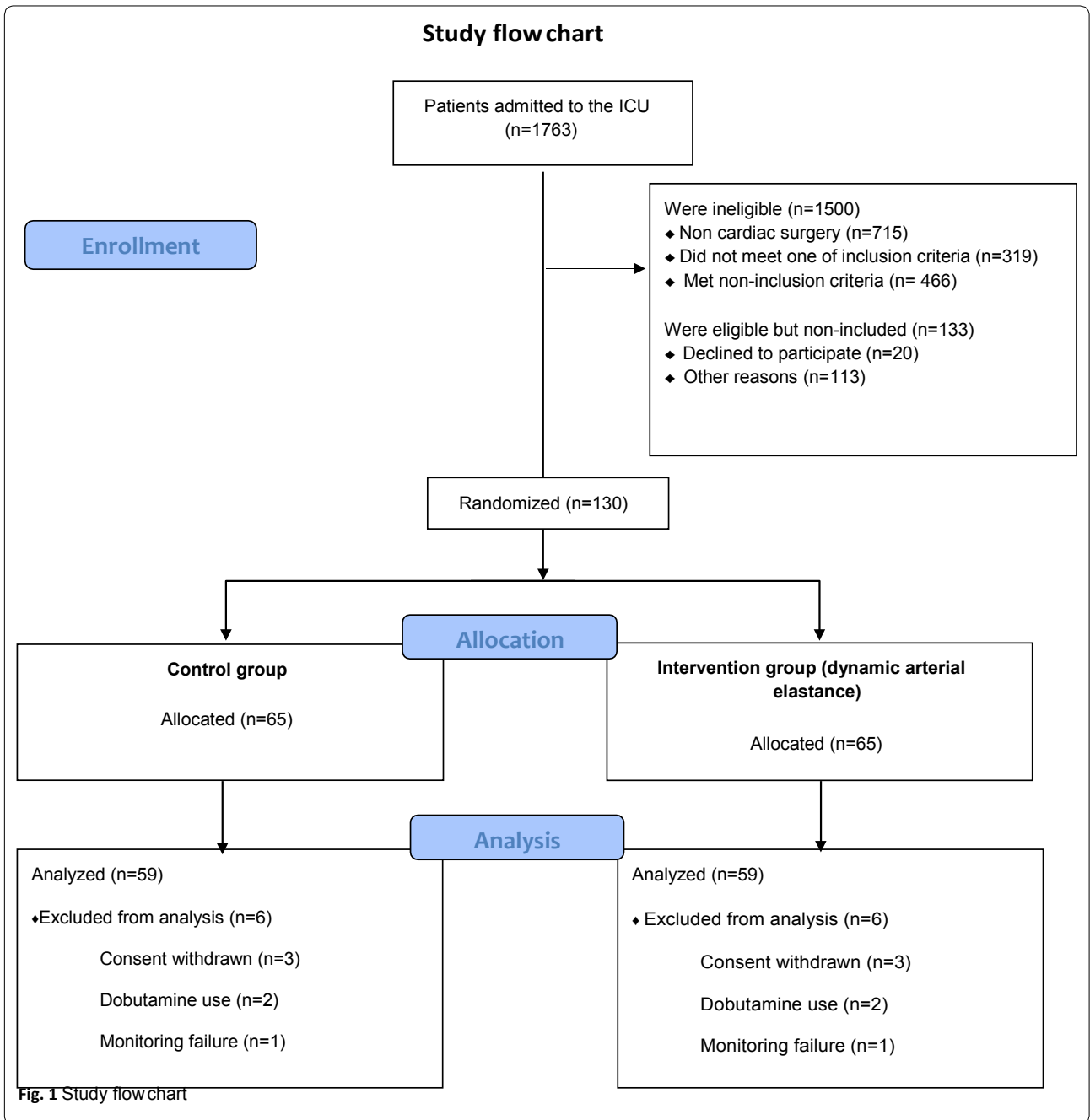


Fig. 1 Study flow chart

**Table 1 Demographic characteristics**

	Control group (n = 59)	Intervention group (n = 59)	P value
Age (years)	66 ± 11	69 ± 11	0.255
Gender (M), n (%)	40 (68)	37 (63)	0.562
BMI (kg m <sup>-2</sup> )	29 (6)	28 (5)	0.119
euroSCORE	6 (4–10)	8 (5–11)	0.138
LogisticeuroSCORE	9 (3.7–31.5)	13.9 (4.2–38.7)	0.333
<b>ASA status score, n (%)</b>			
2	3 (5)	1 (2)	0.522
3	44 (75)	42 (71)	
4	12 (20)	16 (27)	
<b>Medical history, n (%)</b>			
Hypertension	35 (59)	39 (66)	0.513
Coronary artery disease	20 (34)	21 (36)	0.900
COPD	10 (17)	10 (17)	1
Diabetes	20 (34)	15 (25)	0.319
Dyslipidaemia	33 (56)	37 (63)	0.517
Peripheral arterial disease	8 (14)	14 (24)	0.807
<b>Surgery, n (%)</b>			
Valvular (aortic, mitral)	32 (54)	29 (49)	0.947
CABG	12 (20)	14 (24)	
Combined surgery	8 (14)	8 (14)	
Other (myxoma, ascending aorta surgery)	7 (12)	8 (14)	
Preoperative LVEF (%)	59 ± 10	58 ± 12	0.559
<b>Peroperative data</b>			
Duration of CBP (min)	106 (63–140)	103 (71–129)	0.581
Duration of AoC (min)	68 (44–99)	70 (45–90)	0.752
Transfusion, n (%)	17 (29)	11 (19)	0.194

Data are expressed as mean ± standard deviation, median (25th to 75th percentiles) or number (%)

M males, BMI body mass index, ASA American Society of Anesthesiology, COPD chronic obstructive pulmonary disease, CABG coronary artery bypass surgery, LVEF left ventricular ejection fraction, CBP cardiopulmonary bypass, AoC aortic clamping

comparing the intervention group with the control group [6 h (1 to 220) vs 8 h (1 to 114),  $P = 0.437$ ].

In the intervention group, the median  $E_{\text{dyn}}$  was 0.9 (0.8 to 1) at inclusion and 1.2 (1.1 to 1.3) at the end of the study ( $P < 0.001$ ).  $E_{\text{dyn}}$  was not correlated with the norepinephrine dose ( $r = -0.73$ ,  $P = 0.582$ ).

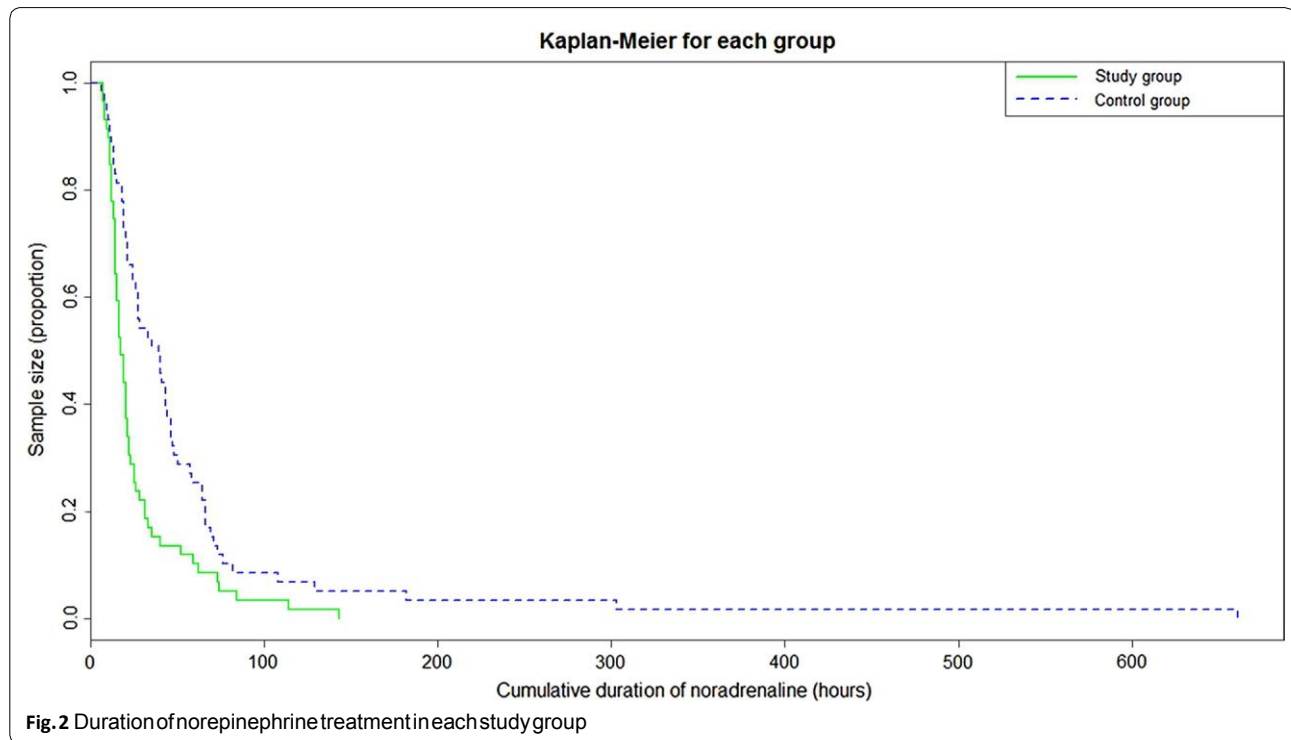
Our main finding was that the total duration of norepinephrine treatment (in hours) was shorter in the intervention group than in the control group values: 17 h (13–26) vs. 39 h (19–58), respectively;  $P < 0.001$  (Fig. 2; Tables 2, 3). The cumulative dose of norepinephrine and the LOS in the ICU were lower in the intervention group than in the control group (Tables 2, 3). There were no intergroup differences in the SOFA score, the arterial lactate concentration or the mortality rate (Tables 2, 3). The intervention and control groups did not differ significantly in terms of the median amount of fluid infused during norepinephrine treatment [1.13 (0.61–1.59) vs. 0.98 (0.52–1.56) ml kg<sup>-1</sup> h<sup>-1</sup>, respectively;  $P = 0.363$ ]

or the median diuresis volume [0.84 (0.56–1.18) vs. 0.71 (0.57–0.89) ml kg<sup>-1</sup> h<sup>-1</sup>,  $P = 0.12$ ].

## Discussion

Our present results demonstrated that the use of an  $E_{\text{dyn}}$ -based haemodynamic monitoring algorithm in the ICU was associated with (1) a shorter duration of norepinephrine treatment, (2) a lower cumulative dose of norepinephrine and (3) a shorter LOS in the ICU. Furthermore, the shorter duration of norepinephrine treatment in the intervention group was not associated with a worsening in perfusion parameters (diuresis, the arterial lactate concentration,  $ScvO_2$  and the SOFA score) or increased fluid infusion.

The present study is the first to have validated the use of  $E_{\text{dyn}}$  as a means of haemodynamically optimizing norepinephrine treatment. This constitutes an individualized approach to patient management, in which the value of conventional vasopressor treatment techniques



**Table 2** Primary and secondary endpoints

	Intervention group (n = 59)	Control group (n = 59)	P value
Duration of norepinephrine treatment at inclusion (hours)	5 (4–10)	5 (5–7)	0.543
Mean norepinephrine dose at inclusion ( $\mu\text{g}^{-1} \text{kg}^{-1} \text{min}^{-1}$ )	0.11 (0.07–0.14)	0.11 (0.06–0.14)	0.527
Total duration of norepinephrine treatment (hours)	17 (13–26)	39 (19–58)	<0.0001
Total norepinephrine administered (mg)	4.96 (0.74–208)	11.40 (1.05–422)	0.015
Total fluid volume infused ( $\text{ml kg}^{-1} \text{h}^{-1}$ )	1.13 (0.61–1.59)	0.98 (0.52–1.56)	0.363
Cumulated diuresis ( $\text{ml kg}^{-1} \text{h}^{-1}$ )	0.84 (0.56–1.18)	0.71 (0.57–0.89)	0.126
Arrhythmia, n (%)	8 (14)	16 (27)	0.067
Deaths, n (%)	2 (3)	2 (3)	1
Length of stay in the ICU (days)	2 (2–3)	3 (2–5)	0.021
Length of stay in hospital (days)	13 (9–19)	14 (10–20)	0.449

Data are expressed as mean  $\pm$  standard deviation, median (25th to 75th percentiles) or number (%)

is subjected to intense scrutiny (as has been already done so for the management of sedation in the ICU) [16]. For many years, early goal-directed therapy (EGDT) has been studied with a view to optimizing the haemodynamic management of high-risk surgical patients or those with acute circulatory failure [17–22]. The implementation of EGDT was shown to decrease mortality and morbidity rates—particularly in high-risk surgical patients [18, 19]. These data have given rise to many different treatment protocols and have been incorporated in guidelines for the haemodynamic management of critically ill patients [20–23]. EGDT only takes account of the speed with

which a predefined haemodynamic goal can be achieved; subsequent haemodynamic management is left to the physician's discretion.

There are few published data on vasopressor weaning [24]. Before  $E_{a_{\text{dyn}}}$  can be applied widely in this context, our results must be validated by further studies in other life-threatening situations (such as sepsis and haemorrhage). Sepsis vasoplegic syndrome may differ from the pathophysiological process, with more pronounced endothelial dysfunction, alterations in oxygen extraction, and the requirement for a higher dose of norepinephrine than vasoplegic syndrome after cardiac surgery. Despite

**Table 3 Changes in the study parameters during the study period**

	Start of norepinephrine administration	Inclusion in the study	End of norepinephrine administration
<b>SOFA score</b>			
Control group	5 (3–8)	7 (6–9)	2 (1–3)
Intervention group	6 (3–8)	8 (7–9)	2 (1–3)
<i>P</i> value	0.461	0.079	0.132
<b>Heart rate (bpm)</b>			
Control group	87 ± 20	87 ± 17	86 ± 16
Intervention group	85 ± 16	86 ± 17	85 ± 16
<i>P</i> value	0.479	0.635	0.725
<b>MAP (mmHg)</b>			
Control group	71 ± 11	77 ± 9	78 ± 8
Intervention group	71 ± 9	76 ± 7	77 ± 6
<i>P</i> value	0.430	0.157	0.407
<b>CVP (mmHg)</b>			
Control group	9 (5–12)	9 (4–12)	8 (7–11)
Intervention group	8 (4–11)	8 (6–10)	9 (6–11)
<i>P</i> value	0.706	0.703	0.571
<b>CI (l min<sup>-1</sup> m<sup>-2</sup>)</b>			
Control group	1.95 ± 0.6	2.2 ± 0.6	2.5 ± 0.6
Intervention group	2 ± 0.4	2.3 ± 0.6	2.7 ± 0.5
<i>P</i> value	0.424	0.456	0.136
<b>Saline solution (ml)</b>			
Control group	250 (0–500)	1000 (500–1250)	2500 (1500–3500)
Intervention group	500 (0–500)	1000 (500–1500)	1500 (750–2250)
<i>P</i> value	0.597	0.877	0.007
<b>Colloid solution (ml)</b>			
Control group	0 (0–0)	0 (0–500)	500 (0–1000)
Intervention group	0 (0–0)	0 (0–300)	0 (0–500)
<i>P</i> value	0.218	0.268	0.052
<b>Transfusion, <i>n</i> (%)</b>			
Control group	5 (8)	9 (15)	23 (38)
Intervention group	4 (7)	9 (15)	15 (25)
<i>P</i> value	1	1	0.055
<b>Cumulative dose of norepinephrine dose (mg)</b>			
Control group	0	1.74 (0.9–5)	11.40 (1.05–422)
Intervention group	0	1.73 (0.9–2.9)	4.96 (0.74–208)
<i>P</i> value		0.223	0.013
<b>Arterial lactate concentration (mmol l<sup>-1</sup>)</b>			
Control group	1.9 (1.3–2.3)	2.1 (1.5–2.5)	1.5 (1.2–1.9)
Intervention group	1.5 (1.2–2.1)	1.9 (1.4–2.5)	1.5 (1.2–2)
<i>P</i> value	0.134	0.469	0.842
<b>ScvO<sub>2</sub> (%)</b>			
Control group	73 ± 11	70 ± 10	68 ± 12
Intervention group	72 ± 12	70 ± 10	72 ± 8
<i>P</i> value	0.532	0.946	0.023
<b>Cumulative diuresis (ml)</b>			
Control group	0 (0–0)	300 (115–645)	2305 (885–3385)
Intervention group	0 (0–0)	305 (142–648)	1362 (784–2181)
<i>P</i> value	0.765	0.846	0.010

Data are expressed as mean ± standard deviation, median (25th to 75th percentiles) or number (%). The *P* value always refers to a comparison between the intervention group and the control group

SOFA sepsis-related organ failure assessment, BPM beats per minute, CI cardiac index, CVP central venous pressure, MAP mean arterial pressure, ScvO<sub>2</sub> central venous saturation

these differences, the clinical expression of vasoplegic syndrome will be arterial hypotension requiring vasopressor treatment.  $E_{a_{dyn}}$  (but not blood pressure or SVR) was able to predict a fall in blood pressure upon norepinephrine weaning in septic patients [13]. Our previous work differed from the present study in that  $E_{a_{dyn}}$  was lower, the patients were treated with higher norepinephrine doses and  $E_{a_{dyn}}$  was not correlated with the norepinephrine dose [13]. The present and previous results suggest that arterial tone is altered more in sepsis than in vasoplegic syndrome after cardiac surgical [13]. Nevertheless, given that  $E_{a_{dyn}}$  is not associated with the norepinephrine baseline dose and changes over time, it could be considered as an independent functional parameter of arterial tone [13, 15]. On the basis of our previous findings in septic patients, we were able to validate  $E_{a_{dyn}}$  in cardiac surgery patients. We believe that  $E_{a_{dyn}}$  could be used to monitor arterial tone in septic patients [25]. The present study should be considered as a validation study that has confirmed the value of individualized optimization of haemodynamics and rapid vasopressor withdrawal.

In contrast to the indices from which  $E_{a_{dyn}}$  is calculated,  $E_{a_{dyn}}$  may have several important advantages in the haemodynamic management of ICU patients. It is an easy-to-measure putative functional parameter of arterial tone. If  $E_{a_{dyn}}$  remains above a defined threshold, it enables vasopressor support to be decreased independently of the arterial pressure values [13, 26]. Spontaneous breathing does not alter the predictability of  $E_{a_{dyn}}$  [11]. Cecconi and colleagues demonstrated the ability of  $E_{a_{dyn}}$  to track arterial tone and predict the blood pressure response to fluid challenge in spontaneously breathing patients [11]. The patients in our present study were extubated;  $E_{a_{dyn}}$  was thus used successively in mechanically ventilated and spontaneously breathing patients, and was found not to be dependent on the ventilation status [11]. Lastly,  $E_{a_{dyn}}$  circumvents a number of important limitations on the use of dynamic indicators of preload dependency, which may facilitate the dissemination and application of this new index. The widespread use of this parameter is possible in operating theatres and ICUs, where haemodynamic optimization represents a daily challenge.

Several limitations may be considered. Firstly, the  $E_{a_{dyn}}$  threshold used in the present work corresponds to that reported in our previous study of septic shock patients [13]. Other researchers have used thresholds that ranged from 0.74 to 1.06 [8, 10–12]. These values are similar to the one we used and may correspond to a grey zone. At the bedside, a threshold close to 1 might facilitate the calculation of  $E_{a_{dyn}}$  with good sensitivity. Although the present study was randomized, it had an open design; this

could introduce bias into the results. Some patients in the control group had radial artery measurements, whereas all patients in the study group had femoral artery measurements. This was due to our decision to use different CO monitoring devices in the control and intervention groups (in order to limit the bias related to real-time respiratory variations in SV and PP values). Mignini and colleagues showed that femoral and radial MAP measurements showed a good level of agreement (regardless of the use of vasoactive drugs) and that the two measurements were interchangeable [27]. As our weaning protocol included the measurement of MAP (but not SAP or DAP), we believe that this type of bias is negligible. One can question the validity of the mathematical coupling equation, since respiratory variations in SV and PP were measured with the same device on the same signal. García and colleagues demonstrated that when calculated from two independent signals,  $E_{a_{dyn}}$  is still predictive of the arterial pressure response to fluid challenge [10]. Since the device was regularly calibrated before and after the changes in norepinephrine treatment, we can reasonably assume that  $E_{a_{dyn}}$  was calibrated for the vascular tone change induced by norepinephrine [28]. To date,  $E_{a_{dyn}}$ 's ability to predict a need for norepinephrine when the index is measured with a non-calibrated pulse contour device has not been validated. Thus, the results presented here correspond solely to the algorithm-based PICCO system. Further studies with other CO monitoring devices are needed. Lastly, we excluded patients treated with dobutamine and/or epinephrine, who may account for up to 30% of the patients in an ICU. Dobutamine has vasodilatory effects that could affect  $E_{a_{dyn}}$ 's predictive value and/or thresholds. In such situations, additional studies are needed to determine the indicator's value in assessing vascular tone and predicting norepinephrine dependency.

## Conclusion

The use of an algorithm based on  $E_{a_{dyn}}$  was associated with a shorter duration of norepinephrine treatment and a lower cumulative dose of norepinephrine in cardiac surgery patients suffering from vasoplegic syndrome. The shorter duration of norepinephrine treatment did not alter perfusion parameters or the fluid requirements. Lastly, optimization of norepinephrine treatment with the  $E_{a_{dyn}}$ -based algorithm was associated with a shorter stay in the ICU.

### Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4666-z) contains supplementary material, which is available to authorized users.

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#### Compliance with ethical standards

#### Conflicts of interests

The authors declare that they have no competing interests.

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### 3. Synthèse et perspectives

Le syndrome vasoplégique est une situation quotidienne pour l'anesthésiste-réanimateur quelle qu'en soit l'étiologie (sepsis, chirurgie, polytraumatisme, hémorragie). L'ensemble des travaux présentés dans cette thèse orientent vers une nouvelle approche de la prise en charge hémodynamique de ces patients et ouvrent de nouvelles perspectives.

Sur le plan physiopathologique, nous confirmons un lien entre un défaut de la vasomotricité lié à la production de NO par l'endothélium et la survenue d'un syndrome vasoplégique. Le syndrome vasoplégique n'est probablement qu'une expression partielle d'une maladie plus large : la dysfonction vasculaire. Ces résultats nous amènent à reconsidérer la prise en charge du syndrome vasoplégique non pas de manière curative mais préventive. Une étude nationale multicentrique visant à construire un score de risque prédictif de la survenue de syndrome est en cours (ISYVACC). De même, notre intérêt se porte sur l'hydroxycobalamine (vitamine B<sub>12</sub>) comme traitement préventif du syndrome vasoplégique. Cette molécule agit comme capteur de radicaux libres. Quelques cas cliniques semblent indiquer un rôle bénéfique sur le tonus vasomoteur lors de l'administration d'hydroxycobalamine (94, 95). En effet, l'hydroxocobalamine est connue pour entraîner une hypertension artérielle (96). Un avantage est le peu d'effets secondaires (contrairement au bleu de méthylène) en dehors d'une coloration des urines et un effet durable avec une administration unique (97).

Sur le plan hémodynamique, nos travaux sur le couplage ventriculo-artériel et l' $E_{a_{dyn}}$  nous amènent à reconsidérer les critères utilisés pour définir un syndrome vasoplégique ainsi que notre compréhension physiopathologique. La définition de ce syndrome est ancienne et basée sur des mesures réalisées avec un cathéter de Swan-Ganz qui présente lui-même des limites. Nos résultats démontrent qu'un certain nombre de patients hypotendus définis comme souffrant d'un syndrome vasoplégique donc traités par noradrénaline présentaient un découplage en rapport avec une atteinte de la fonction cardiaque plutôt que la fonction vasculaire, alors même que la FeVG ne semblait pas suffisamment altérée pour expliquer cet état hémodynamique. La noradrénaline restaurait la pression artérielle par une réponse hémodynamique plutôt en rapport avec ses effets inotropes. Donc, ces patients ne présentaient pas à proprement parler un syndrome vasoplégique mais plutôt une ICA

cardiogénique. De ce fait, une série d'études va être mise en place en multicentrique afin d'évaluer et de caractériser l'hypotension artérielle persistante et sa réponse au traitement, au bloc opératoire et en réanimation selon les deux approches complémentaires de l'évaluation hémodynamique : Franck-Starling-Guyton et le couplage ventriculo-artériel. D'autre part, nous travaillons sur une mesure non-invasive et continue du couplage ventriculo-artériel par bioimpédancemétrie.

Un dernier point soulevé par ces travaux est l'étude et la validation d'un nouvel indice de charge artérielle : l'élastance artérielle dynamique. Peu de données existent actuellement sur la signification physiologique exacte de cet indice. L' $E_{a_{dyn}}$  est validée comme prédictive de la dépendance de la pression artérielle à un vasopresseur. Les résultats sur la prédiction d'une augmentation de la pression artérielle avec le remplissage vasculaire sont plus inconstants (98, 99). Une étude récente soulève la possibilité que l' $E_{a_{dyn}}$  reflète le couplage ventriculo-artériel en raison de son association à des facteurs cardiaques et vasculaires (38). Notre équipe a mis en place une série de travaux dont l'objet est d'approfondir notre connaissance physiologique sur cet indice. Parmi celles-ci, une étude en cours évalue l' $E_{a_{dyn}}$  comme indice de couplage ventriculo-artériel chez des patients avec un syndrome vasoplégique. Ce travail ne démontre pas d'association entre les paramètres de couplage ventriculo-artériel et l' $E_{a_{dyn}}$ . Une autre étude pose l'hypothèse que l' $E_{a_{dyn}}$  serait un reflet du couplage entre la macrocirculation et la microcirculation (Etude Poeme en cours). Une dernière série d'études va essayer de déterminer la place de l' $E_{a_{dyn}}$  dans l'optimisation hémodynamique péri-opératoire en l'intégrant dans des algorithmes décisionnels lors d'hypotension artérielle.



#### **4. Conclusions**

Le syndrome vasoplégique est une situation quotidienne pour l'anesthésiste-réanimateur quelle qu'en soit l'étiologie (sepsis, chirurgie, polytraumatisme, hémorragie). L'ensemble des travaux présentés dans cette thèse ouvre une nouvelle approche de la prise en charge de ce syndrome hémodynamique. Ces études soulignent l'impact clinique positif en repositionnant notre « regard de l'hémodynamique » selon une approche dynamique par la mesure de l'élastance artérielle dynamique et du couplage ventriculo-artériel.

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