

# Quantitative assessment of reflux in commercially available needle-free IV connectors

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## ABSTRACT

**Introduction:** Blood reflux is caused by changes in pressure within intravascular catheters upon connection or disconnection of a syringe or intravenous tubing from a needle-free connector (NFC). Changes in pressure, differing with each brand of NFC, may result in fluid movement and blood reflux that can contribute to intraluminal catheter occlusions and increase the potential for central-line associated bloodstream infections (CLABSI).

**Methods:** In this study, 14 NFC brands representing each of the four market-categories of NFCs were selected for evaluation of fluid movement occurring during connection and disconnection of a syringe. Study objectives were to 1) theoretically estimate amount of blood reflux volume in microliters ( $\mu\text{L}$ ) permitted by each NFC based on exact component measurements, and 2) experimentally measure NFC volume of fluid movement for disconnection reflux of negative, neutral and anti-reflux NFC and fluid movement for connection reflux of positive displacement NFC.

**Results:** The results demonstrated fluid movement/reflux volumes of 9.73  $\mu\text{L}$  to 50.34  $\mu\text{L}$  for negative displacement, 3.60  $\mu\text{L}$  to 10.80  $\mu\text{L}$  for neutral displacement, and 0.02  $\mu\text{L}$  to 1.73  $\mu\text{L}$  for pressure-activated anti-reflux NFC. Separate experiment was performed measuring connection reflux of 18.23  $\mu\text{L}$  to 38.83  $\mu\text{L}$  for positive displacement NFC connectors.

**Conclusions:** This study revealed significant differences in reflux volumes for fluid displacement based on NFC design. While more research is needed on effects of blood reflux in catheters and NFCs, results highlight the need to consider NFCs based on performance of individual connector designs, rather than manufacturer designation of positive, negative and neutral marketing categories for NFCs without anti-reflux mechanisms.

**Keywords:** Intravenous catheters, Needleless connectors, Occlusion, Reflux

## Introduction and background

Prior to the advent of needle-free connectors (NFCs), stainless-steel needles were used to access intravenous (IV) y-sites, tubing ports and injection sites. While this process was effective for IV pathway access, needle-stick injuries became a substantial risk to healthcare workers, increasing the potential for occupationally acquired blood-borne diseases (1). In 1992, the Occupational Safety and Health Administration (OSHA) recommended that healthcare facilities incorporate “engineering controls” to prevent such occurrences (2).

The use of “engineering controls” included the integration of NFCs into the IV access system both for needle safety and for the prevention of central-line associated bloodstream infections (CLABSI) (3-5). NFCs allow for the administration of IV fluids, medications and blood to indwelling venous or arterial catheters without the use of needles. NFCs are also used for the withdrawal of blood samples and for aspiration of blood to check the catheter for patency. While the introduction of NFCs greatly reduced the risk of needle-stick injuries for healthcare workers, their use has been associated with other complications such as an increase in catheter occlusions and CLABSIs (6-11).

In response to the increase in CLABSI related to the use of NFCs, medical device companies began designing and developing lower-risk devices (12). Over the past 20 years, 4 categories of NFC designs have emerged (2, 13). While there is no regulatory body that recognizes the categories of NFC as being indicative of function or performance (13), NFCs are typically marketed as being “positive”, “negative”, “neutral” (6, 12-16) or pressure-activated anti-reflux (9, 13, 17). The characteristics of each category of NFC indicate the mechanism and action of the NFC upon connection/disconnection.

Accepted: June 13, 2017

Published online: December 4, 2017

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**TABLE I** - Fluid displacement characteristics of negative, neutral displacement, pressure activated anti-reflux, and positive, needle-free connectors

Types of NFCs	Negative displacement NFC	Neutral displacement NFC	Anti-reflux NFC	Positive displacement NFC
Fluid movement upon disconnection	Blood refluxes into catheter	Blood refluxes into catheter	Fluid restricted by diaphragm	Fluid moves toward patient
Fluid movement upon connection	Fluid moves toward patient	Fluids moves toward patient	Fluid restricted by diaphragm	Blood refluxes in to catheter
Manufacturer recommended clamping sequence	Clamp before disconnection	No specified clamping	No specified clamping	Clamp after disconnection of male luer

NFCs are designed as end caps to lock/luer onto the hub of catheters. Efficiency may be measured on the ability of the NFC design to prevent movement of fluids and inadvertent reflux of blood into the catheter (18, 19). The key features and defining characteristics of each NFC design along with manufacturer recommended clamping sequences are summarized in Table I. The specifics of each type of NFC are further explored in the *Discussion* section of this paper.

Unfortunately, the large variety of NFCs, the different designs, performance and instructions for use with each device is a source of confusion among clinicians. In a 2011 survey of 4000 healthcare workers in which 554 responded (9):

- 21.9% did not know which brand of needle-free IV connector was used with their CVCs (2)
- 25.4% did not know if their connector was 'positive', 'negative' or 'neutral' (2)
- 47.2% did not understand the correct way to flush and clamp a catheter with the NFC used by their institution (9).

It is not uncommon for several types or brands of NFCs to be used on peripheral and central venous access devices within a single hospital, such as one category for peripheral catheters and a different category for central catheters (2, 6, 9). Evidence suggests that lack of training for device usage correlates with an increase in CLABSI (20). This was demonstrated in a 2009 study that followed five hospitals adopting new NFCs (12). When switching NFC brands from 'negative' to 'positive' connectors, which may have different instructions for use, some hospitals reported an increase in bloodstream infections (8). However, hospitals that went back to their original NFC subsequently reported infection rates had returned to previous levels (8, 15, 21). This evidence suggests that NFC design differences, variations in instructions for use and inconsistencies in aseptic technique may contribute to increased incidence of CLABSI associated with NFCs (2, 8, 9, 12).

Central venous access devices (CVAD) have undergone design changes; some of these changes included the elimination of clamps. Despite the instructions for use of many NFC manufactures to use clamps on catheters after disconnection, the option to perform this action is often not present (22).

Given the inconsistencies noted with NFC usage, the aim of the research was to clarify NFC function by quantifying

fluid movement and volume of reflux occurring within each NFC after disconnection or connection.

## Materials and methods

For this study, 14 commercially available NFCs were selected to quantitatively study the fluid reflux volume in microliters ( $\mu\text{L}$  or  $\text{mm}^3$ ) of each NFC. Study objectives were to (i) theoretically estimate amount of blood reflux volume in microliters ( $\mu\text{L}$ ) permitted by each NFC based on exact component measurements, and (ii) experimentally measure amount of fluid movement or reflux. The 14 NFCs are represented in each of the four current marketing categories of NFC (13). The NFCs selected for evaluation in this study included:

### Negative displacement

- BD Carefusion Smartsite
- BD Q-Syte
- Baxter Interlink
- ICU Medical Clave\*

### Neutral displacement

- ICU Medical Microclave Clear
- Baxter One-Link
- RyMed Invision
- Nexus NIS-6P

### Pressure activated anti-reflux

- ICU Medical Neutron
- Nexus TKO-5
- Nexus TKO-6P

\*ICU Medical Clave is included in the negative displacement NFC group based on terminology and grouping established in prior publication (13).

### Positive displacement\*

- B. Braun Ultrasite
- BD Carefusion MaxPlus
- B. Braun Caresite

\*As defined in publications as positive pressure mechanical valve with reflux occurring on connection with a final fluid push at disconnection clearing blood from catheter tip, described as a compression/decompression mechanism creating positive (disconnection) and negative pressure (on activation) resulting in fluid displacement fluctuations (2, 16).

To meet the goals of this study, two independent experiments were performed, with experiment 2 separated into 2A and 2B to clearly separate differences of positive displacement devices from negative, neutral and anti-reflux NFC.

### Experiment 1: theoretical estimates of NFC reflux volume (Fig. 1)

#### Purpose

To calculate the amount of blood reflux created by suction pressure which occurs in NFC designs.

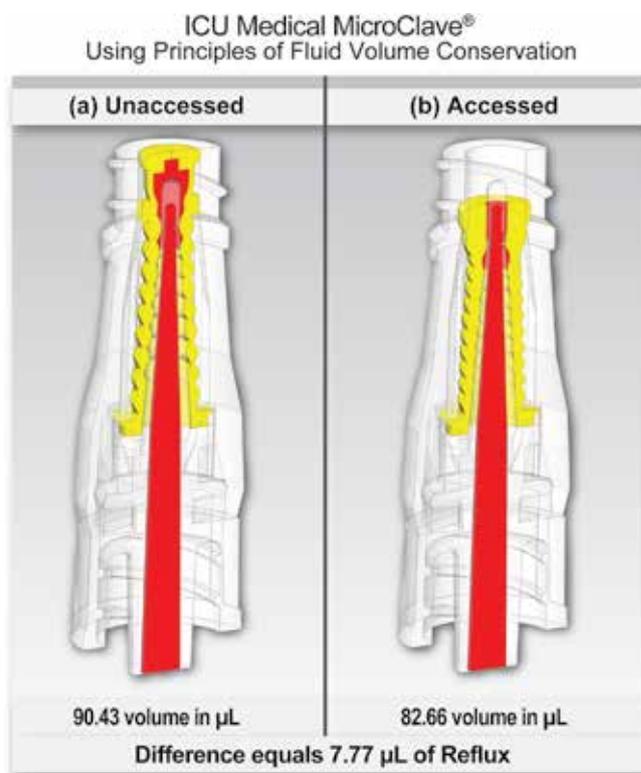
#### Materials

- Computer with SolidWorks® Professional 2015 software
- OGP SmartScope Flash 200 Optical Comparator Measurement System
- SolidWorks CAD models of each NFC

#### Method

To estimate the amount of blood reflux caused by suction pressure during periods of compression and subsequent non-compression from syringe connection and disconnection, dimensions of each component of all NFCs were precisely measured using a computerized optical measuring system (OGP SmartScope Flash 200) by Simplificated Innovation LLC. Each component of the NFC was precisely dimensioned ( $\pm 0.001''$ ) and built into 3-dimensional (3-D) model using Computer Aided Design (CAD) 3-D software (SolidWorks™ Professional 2015). These dimensions provided the necessary input for the computational study and the elastomeric compression in Experiment 1. Geometrical and mass property calculations were used to generate data measuring the mechanical reflux created during compression of the soft septum during the connection and disconnection of a male luer locking syringe to each NFC septum.

Two pictorial models were created for each NFC using SolidWorks modeling tools: the first was a 'un-accessed' or un-compressed "at rest" representation in which the NFC is not connected to a male luer from the syringe or IV tubing set. The second picture demonstrates what happens when the same NFC is 'accessed' by a male luer connector, showing compression of the soft septum, the corresponding movement inside the NFC, and the resulting suction pressure and fluid reflux or flow. For this experiment, a 10-mL BD syringe or a blunt cannula was used (Fig. 1). The volume of the "accessed" and "un-accessed" 3-D models were calculated. Subtracting the volume of the "un-accessed" or uncompressed "at rest" area from the "accessed" or compressed area of the NFCs produces the theoretical amount of fluid displacement available to reflux into an IV catheter upon connection or disconnection of the male luer.



**Fig. 1** - Experiment 1 - Pictorial model of a needle-free connector (MicroClave®) showing its internal mechanism when (A) unaccessed and (B) accessed using a 10-mL BD Syringe. Internal fluid pathway is displayed in red, moving silicone parts in yellow, and the outer housing as translucent. Below the images are the corresponding volumes of the fluid pathway and the differences between them, which yield the expected volume of reflux (reflux volumes for the other NFCs were calculated in a similar manner).

Theoretical calculations of reflux values obtained for each of the 14 connectors are listed in Table II.

### Experiment 2A: Actual venous simulation of negative, neutral and anti-reflux NFC reflux volume (Tab. II)

#### Purpose

Quantify the amount of fluid movement or reflux associated with the disconnection (negative, neutral and anti-reflux NFC) of a male luer lock to each of the 11 (of 14) NFCs.

To measure blood reflux or fluid movement associated with each NFC upon disconnection of a male luer, an in vitro venous model was created in the laboratory using the following:

#### Materials (Fig. 2)

- An industry standard 10-mL syringe (BD Luer-Lok™ tip syringe)
- Needle-free connectors (NFCs)
- Clear PVC tubing and stopcock
- Glass capillary rod (6 mm OD × 1.2 mm ID × 12")

**TABLE II** - Results of the theoretical calculations and actual in vitro venous values

NFC category	Brand	Experiment 1: theoretical calculations ( $\mu\text{L}$ )	Experiment 2: actual in vitro venous values ( $\mu\text{L}$ )	SD
Negative	Carefusion Smartsite®	27.92	50.37	1.069
	BD Q-Syte®	23.20	38.34	0.721
	Baxter Interlink®	11.98	13.18	0.134
	ICU CLAVE®	8.02	9.73	0.265
Neutral	ICU MicroClave®	7.77	10.80	0.458
	Baxter One-Link®	15.87	8.05	0.058
	Rymed InVision	2.93	6.54	0.375
	Nexus NIS®-6P	5.21	3.60	1.487
Anti-reflux	ICU Neutron™	5.21	1.73	2.656
	Nexus TKO®-5	4.03	0.34	0.661
	Nexus TKO®-6P	5.26	0.02	0.029
Positive	B. Braun Ultrasite®	59.69	38.83	2.619
	Carefusion MaxPlus®	75.81	23.73	1.872
	B. Braun Caresite®	10.65	18.23	4.604

For Experiment 1, “theoretical” values are in microliter ( $\mu\text{L}$ ) volumes mathematically calculated using the method shown in Figure 1. For Experiment 2, actual in vitro venous values in microliter ( $\mu\text{L}$ ) volumes are the results from fluid reflux obtained upon disconnection of negative, neutral displacement and pressure activated anti-reflux NFCs and upon connection for positive displacement NFC.

NFC = needle-free connector; SD = standard deviation.

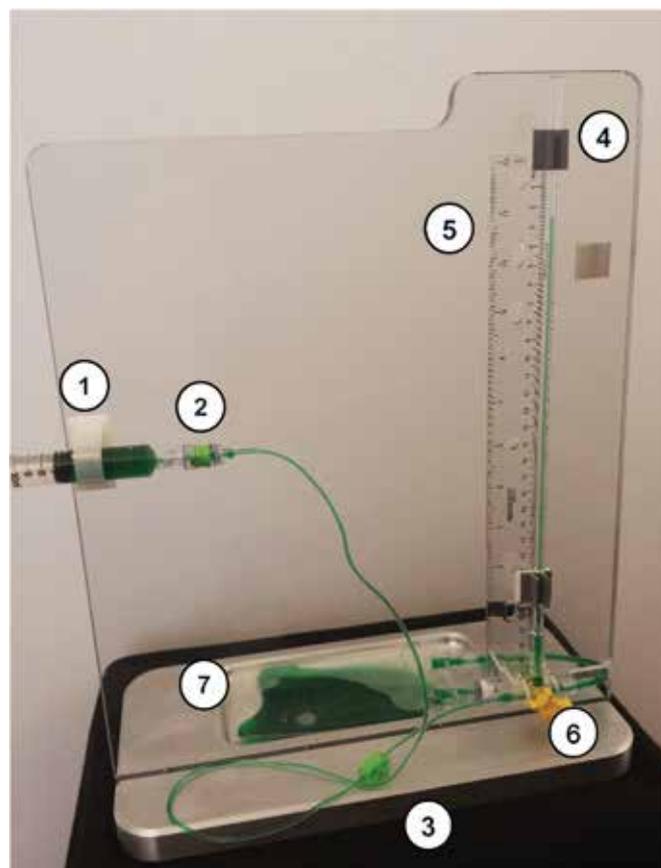
- Metric ruler
- Collection bag with water (green food coloring added).

### Method

The in vitro venous model was designed to replicate the conditions which cause blood reflux into an IV catheter during disconnection of a syringe from an NFC. This venous simulation apparatus was designed to replicate the peripheral venous pressure found in the human vasculature (2, 23). For the purposes of this study, an average venous pressure of 8 mmHg was used. A glass capillary rod was used to allow for visualization as well as accurate measurement of fluid movement.

For the categories of negative displacement, neutral displacement and pressure-activated anti-reflux NFCs (Fig. 2), each of the NFCs was connected to the PVC tubing, which was attached to a stopcock and the vertically positioned glass capillary rod on the model. The following procedure was performed a total of 30 times per NFC type and brand:

1. A 10-mL syringe was filled with water and attached directly to the NFC.
2. The stopcock on the model was turned “OFF” to the glass capillary tube.



**Fig. 2** - In vitro venous model used to measure actual reflux. Consists of the following: (1) Standard 10-mL BD Luer Lock syringe, (2) Needle-free connector, (3) Clear PVC tubing, (4) Glass capillary rod, (5) Metric ruler, (6) 3-way stopcock, (7) Collection bag with dyed water.

3. The 10-mL syringe plunger was depressed and all air was purged from the NFC, PVC tubing and stopcock attached to the model.
4. The stopcock was turned “ON” to the glass capillary rod.
5. The syringe plunger was slowly depressed allowing fluid to fill the glass capillary rod until the fluid level reached 108 mm (equal to 8 mmHg of simulated venous pressure) on the metric ruler.
6. The syringe was disconnected from the NFC and the amount of fluid reflux in the glass capillary tube was recorded.

Three sterile samples of each NFC were tested; steps 1-6 were repeated 10 times for each sample for a total of 30 venous simulations per NFC. All 30 tests were totaled and averaged to obtain a statistically significant total fluid reflux distance into the glass capillary rod. In this study, all experiments were conducted by one person, minimizing user variances, resulting in relatively low standard deviations.

The inside diameter of the glass capillary rod is 0.60 mm. The average distance of fluid reflux volume of each of the 14 NFCs was used to calculate the total reflux volume in microliters ( $\text{mm}^3$  or  $\mu\text{L}$ )

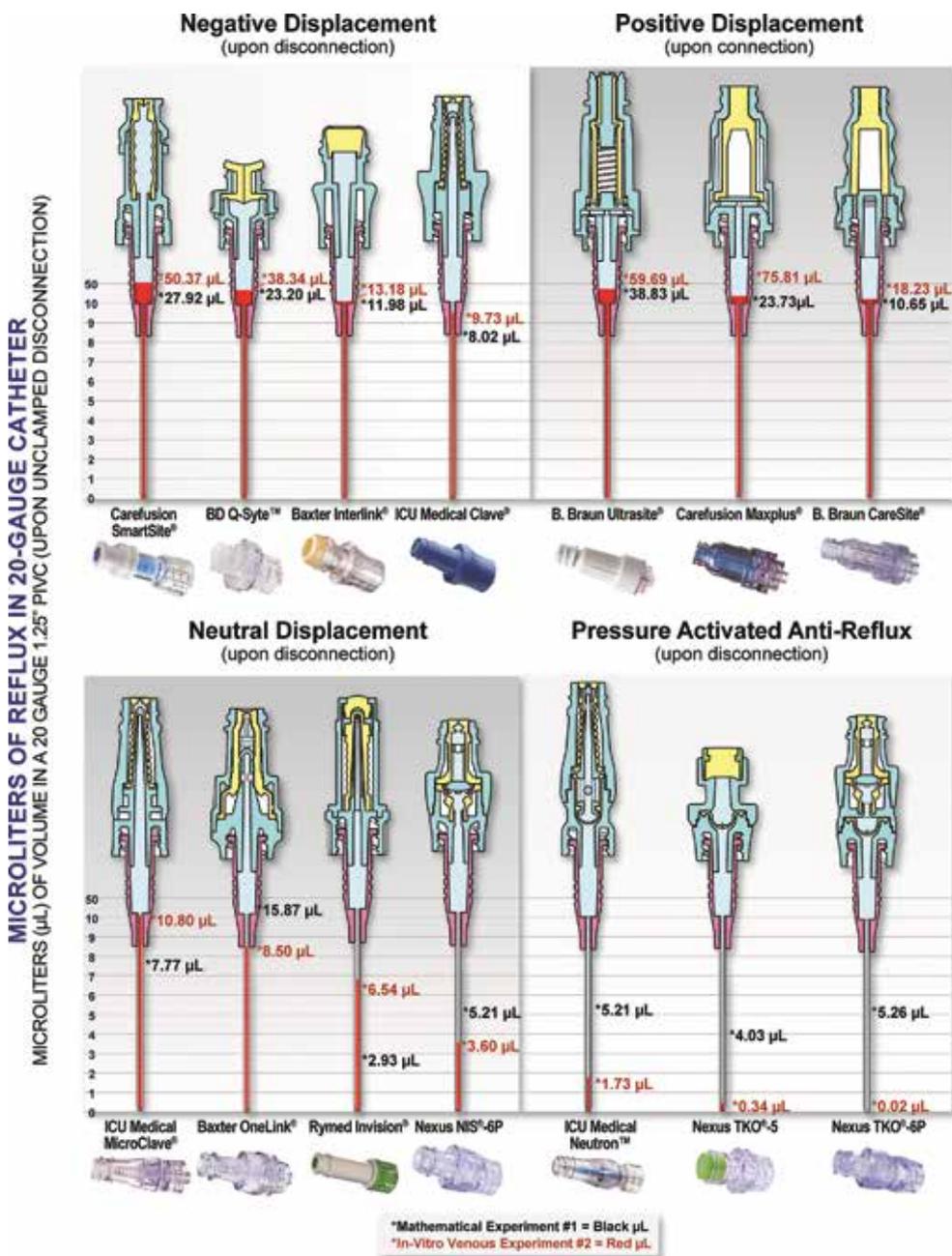


Fig. 3 - Visual representation of the consequences of reflux into a 20-gauge catheter lumen using the Experiment 1, theoretical/mathematical calculations and Experiment 2, actual in vitro venous values. The individual pictures of each NFC illustrate the distance in microliters (µL) the amount of blood can reflux into the catheter using both the theoretical/mathematical Experiment 1 (black) and actual in vitro venous value Experiment 2 (red). On each of the cross-sectional views, the volume of blood reflux is depicted in red. Each NFC illustration shows the silicone elastomeric septum in yellow, outer NC housings in blue and fluid pathway in light blue.

$$V = \pi r^2 h$$

V = volume, r = radius, and Δh = change in height.

Figure 3 provides a visual representation of the venous simulation experimental reflux values as they appear inside a 20-gauge catheter connected to the respective NFC, illustrating the implications of fluid movement and reflux within a catheter.

### Results of disconnection displacement

Four-hundred and twenty NFC fluid displacement measurements were performed in vitro for negative, neutral and anti-reflux NFC (30 actuations for each of the first 11 NFCs,

with a total of 14 NFCs for both experiments 2A and 2B). The complete results of theoretical and actual venous simulation of fluid reflux are displayed in Table II. The results for the three categories of negative, neutral and anti-reflux NFC were reported per NFC, per category and in ranges of theoretical and actual. In the negative displacement group fluid displacement volumes were ranging from 9.73 to 50.37 µL for all NFCs. This negative displacement group represented the widest range of values in comparison to the four categories. The theoretical calculations were lower than the actual results by 10%-80%, with standard deviation.

Table III represents the mean results of the top five performing NFCs as predicted by the quantitative analysis versus actual reflux volumes based on the in vitro experiment.



**TABLE III** - Mean results of the top five performing NFCs

Predicted volumes ( $\mu\text{L}$ )		Actual volumes ( $\mu\text{L}$ )	
Model	Reflux volume	Model	Reflux volume
Rymed InVision	2.93	Nexus TKO-6P	0.02
Nexus TKO-5	4.03	Nexus TKO-5	0.34
Nexus NIS 6P	5.21	ICU Neutron	1.73
ICU Neutron	5.21	Nexus NIS 6P	3.60
Nexus TKO-6P	5.26	Rymed InVision	6.54

Predictors of quantitative analysis versus actual reflux volumes of in vitro experiments.

**TABLE IV** - Predicted versus actual reflux volumes of the lowest five performers

Predicted volumes ( $\mu\text{L}$ )		Actual volumes ( $\mu\text{L}$ )	
Model	Reflux volume	Model	Reflux volume
BD Carefusion MaxPlus	75.81	BD Carefusion Smartsite	50.37
B. Braun Ultrasite	59.69	B. Braun Ultrasite	38.83
BD Carefusion Smartsite	27.92	BD Q-Syte	38.34
BD Q-Syte	23.20	BD Carefusion MaxPlus	23.73
Baxter One-Link	11.98	B. Braun Caresite	18.23

Predictors of quantitative analysis versus actual reflux volumes of in vitro experiments with NFCs allowing the most reflux.

Similarly, Table IV lists the predicted versus actual reflux volumes of the bottom five performers (NFCs allowing the most amount of reflux).

Figure 4 lists the reflux volume range per NFC design category from Table II.

### Experiment 2B: Actual venous simulation of positive pressure NFC reflux volume (Tab. II)

#### Purpose

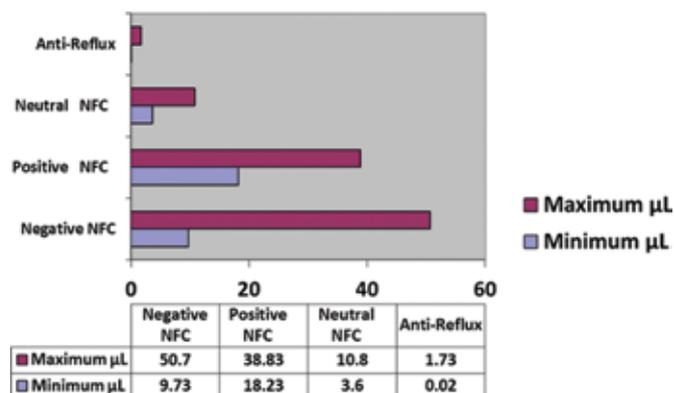
Quantify the amount of fluid movement or reflux associated with the connection of a male luer lock to each of three positive pressure NFC connectors.

To measure blood reflux or fluid movement associated with each positive displacement NFC upon connection of a male luer, an in vitro venous model was created in the laboratory using the following:

#### Materials (Fig. 2)

- An industry standard 10-mL syringe (BD Luer-Lok™ tip syringe)

Needleless connector design	Range of reflux
Negative displacement	9.73 $\mu\text{L}$ to 50.37 $\mu\text{L}$
Neutral displacement	3.60 $\mu\text{L}$ to 10.80 $\mu\text{L}$
Pressure activated anti-reflux	0.02 $\mu\text{L}$ to 1.73 $\mu\text{L}$
Positive displacement	18.23 $\mu\text{L}$ to 38.83 $\mu\text{L}$



**Fig. 4** - Reflux volume range per needle-free connector (NFC) design category from Table II.

- Needle-free connectors (NFCs)
- Clear PVC tubing and stopcock
- Glass capillary rod (6 mm OD  $\times$  1.2 mm ID  $\times$  12")
- Metric ruler
- Collection bag with water (green food coloring added).

#### Method

The in vitro venous pressure model was designed to replicate the conditions that cause blood reflux into an IV catheter during connection of a syringe from each NFC. This venous simulation apparatus/model was designed to replicate the peripheral venous pressure found in the human vasculature (2, 23). For the purposes of this study, an average venous pressure of 8 mmHg was used. A glass capillary rod was used to allow for visualization as well as accurate measurement of fluid movement.

For the category of positive displacement NFCs:

To effectively test reflux, due to the design and functionality of the positive displacement NFCs, the testing was reversed from the test steps above to measure connection reflux (16). Each of the positive displacement NFCs were connected to the PVC tubing attached to a stopcock and the vertical glass capillary rod on the model. The following procedure was performed a total of 30 times per NFC brand:

- A 10-mL syringe was filled with water and attached directly to the NFC.
- The stopcock on the model was turned "OFF" to the glass capillary tube.
- The 10-mL syringe plunger was depressed and all air was purged from the NFC, tubing and stopcock on the model.
- The stopcock was turned "ON" to the glass capillary rod.
- The syringe plunger was slowly depressed allowing fluid to fill the glass capillary rod until the fluid level reached

- 108 mm (equal to 8 mmHg of simulated venous pressure) on the metric ruler.
6. The syringe was disconnected from the NFC and the amount of fluid in the glass capillary tube was recorded.
  7. The syringe was again connected to the positive displacement NFC and the amount of fluid reflux in the glass capillary tube was recorded.

Three samples of each NFC were tested; steps 1-7 were repeated 10 times for each sample for a total of 30 venous simulations per NFC.

All 30 tests were totaled and averaged to obtain a statistically significant total fluid reflux distance into the glass capillary rod. In this study, all experiments were conducted by one person, minimizing user variances, resulting in relatively low standard deviations.

The inside diameter of the glass capillary rod is 0.60 mm. The average distance of fluid reflux volume of each of the 14 NFCs was used to calculate the total reflux volume in microliters ( $\text{mm}^3$  or  $\mu\text{L}$ )

$$V = \pi r^2 h$$

$V$  = volume,  $r$  = radius, and  $\Delta h$  = change in height.

Figure 3 provides a visual representation of the venous simulation experimental reflux values as they appear inside a 20-gauge catheter connected to the respective NFC, illustrating the implications of fluid movement and reflux within a catheter.

## Results of positive displacement

Four-hundred and twenty NFC fluid displacement measurements were performed in vitro (30 for each of the 3 positive pressure NFCs). The complete results of theoretical and actual venous simulation of fluid reflux are displayed in Table II. The results for the last category of positive NFC were reported in ranges of theoretical and actual. In the positive displacement group were fluid displacement volumes ranging from 18.23-38.83  $\mu\text{L}$  with displacement reflux occurring upon connection. This positive displacement group represented a narrow range of values in comparison to the other three categories. The theoretical calculations were generally higher for this group than the actual results by approximately 35%, apart from the B. Braun Caresite where the theoretical calculation was approximately 41% lower than the actual (Tab. II).

Table III represents the mean results of the top five performing NFCs as predicted by the quantitative analysis versus actual reflux volumes based on the in vitro experiment.

Similarly, Table IV lists the predicted versus actual reflux volumes of the bottom five performers (NFC allowing the most amount of reflux).

Figure 4 lists the reflux volume range per NFC design category from Table II.

## Discussion

All NFCs have some fluid movement/reflux either on connection, disconnection or both (16). In this study, we chose to measure the fluid movement for each category of connector

to provide comparison of potential blood reflux. It is not known how long it takes for undisturbed blood in an NFC or catheter to coagulate. It is not known the minimum blood volume that will occlude an intravenous catheter. These issues are the subject of future study. The function of negative, neutral and anti-reflux NFC is consistent with the fluid shift occurring primarily at discontinuation. Positive displacement NFCs have a different function with a mechanical valve that required measurement of the fluid movement at a different stage. In the positive displacement NFC, the fluid shift upon disconnection is offset by the outward displacement of fluid, different from negative and neutral NFCs. This difference in the positive displacement NFC required the fluid displacement measurements to be performed at the time of connection, rather than disconnection. Since intravenous devices with positive displacement NFCs continue to have an incidence of occlusion with the catheters, the hypothesis was that significant reflux occurred at some point of connection or disconnection, or even after the positive pressure push of fluid, justifying the measurement and comparison with another NFC. The researchers recognize that this created a variation, which should be considered as a significant variable in comparisons between each of the NFC categories represented in this study. Since all NFCs have some fluid shift that may result in blood reflux upon connection and/or disconnection these measurements do provide value in comparison, but require an understanding of the distinction between the categories and NFC functions which may not facilitate an exact correlation.

The design of NFC has a significant impact on the ability to clear blood and control reflux. Blood provides many of the nutrients to support the growth of bacteria. Residual blood inside the fluid pathway of an NFC has the potential to increase the risk of occlusion of the device and may promote bacterial growth (2, 24, 25). Each of the NFCs tested in this study was designed to function in a specific way, leading it to be classified as negative, positive, neutral or anti-reflux. For the purposes of this study, the NFCs were categorized based on design and function. A brief description follows:

*Negative displacement* NFCs allow fluid displacement into the catheter lumen during disconnection from a male luer syringe or IV tubing. This displacement occurs when fluid (blood) is mechanically pulled away from the patient and into the catheter or NFC lumen based on pressure changes (9, 13). Because blood is pulled toward the NFC through the catheter upon disconnection, protocol states the catheter be clamped prior to luer-lock disconnection (2, 6, 14). Apart from blunt cannulas entering a split-septum, the general mechanism consists of a plunger depressing a pre-slit septum facilitating fluid flow through the center of the device (6, 26).

*Positive displacement* NFCs allow fluid displacement into the catheter lumen during connection of a male luer syringe or IV tubing. Fluid movement or reflux occurs upon connection with suction created as the syringe is pushed into the NFC. Upon disconnection of the syringe from the NFC a final fluid push/displacement or fluid movement occurs out as a function of the positive displacement NFC (27). Several functional characteristics of positive NFCs differ from other NFCs. For example, while an elastic or deformable plunger is still depressed during luer-lock connection, the fluid flow occurs

around the plunger (6, 26). This space between the plunger and outer housing creates a reservoir where fluid is gathered; when the NFC is disconnected from a syringe or IV tubing, fluid movement occurs and is pushed outward, toward the patient (13). This design is created to overcome potential blood reflux that occurs upon disconnection, but does not prevent fluid displacement associated with connection (13). Theoretically, reflux in positive NFCs may also occur after the fluid push occurs on disconnection, first shifting fluid out and then retracting fluid back. The method to prevent the potential fluid movement after the outward push of fluid with disconnection is through clamping (6, 14, 15). Measurement of pressure variations of positive displacement NFCs was only performed in this study upon connection, not after positive fluid disconnection.

*Neutral displacement* NFCs suggest the absence of fluid movement upon connection or disconnection. The marketing term neutral indicates prevention of blood reflux that is not substantiated in other research (18). The name 'neutral NFC' inherently suggests that these devices eliminate movement of fluid typically observed in negative and positive NFCs (13, 26). However, the internal mechanisms that govern function of when and how fluid movement and flow is established appear to be like those of other negative NFCs (13, 18).

*Anti-reflux* NFCs suggest minimal fluid movement upon connection or disconnection. The function of an anti-reflux NFC is through a 3-position silicone diaphragm, which opens and closes based upon fluid or infusion pressure. The anti-reflux diaphragm opens or closes based on fluid pressure changes from sources such as IV pump, IV bag, when flushing with a syringe or from physiologic body pressure changes (13, 17). Fluid movement and blood reflux is minimized with connection or disconnection of a male luer syringe or IV tubing. The diaphragm within the anti-reflux NFC supports continuous bi-directional fluid pressure control when attached to the hub of a catheter. When the fluid pressure drops, the anti-reflux diaphragm closes preventing blood reflux into the catheters. NFCs designed with an anti-reflux diaphragm provide continuous fluid control while attached to the catheter.

This study sought to quantitatively evaluate fluid reflux within NFCs. The results demonstrate a wide range of displacement in different NFCs ranging from 10-50  $\mu\text{L}$  for 'negative' NFCs, 3-10  $\mu\text{L}$  for 'neutral' NFCs, and displacement that approaches 0 with a range of 0.02-1.73 with pressure activated anti-reflux NFCs. Recent research validates the results with similar findings on some of the included NFCs (20). Of the commercially available NFCs tested in Experiment 2, pressure-activated anti-reflux NFCs performed best in terms of minimizing fluid displacement. The results suggest NFC designs and functional variations represent potential clotting risk associated with blood reflux.

Data shown in Table II and Figure 3 demonstrate the following:

1. All needless connectors have a measurable volume of reflux on connection or disconnection, however small.
2. The amount of reflux within a catheter is dependent on the individual design of the NFC.

3. The type of NFC device (negative, positive and neutral) does not inherently guarantee against unintended or uncontrolled fluid movement or reflux of blood.
4. Anti-reflux connector had the lowest measurable volume of fluid movement.

### **Clinical implications**

Blood reflux volumes as small as 4-30  $\mu\text{L}$  may result in fibrin formation adequate to occlude the function of a catheter (28). Body movements, muscle flexing, respirations, coughing, vomiting, crying, clamping, unclamping, syringe plunger rebound, and connection/disconnection of syringes all cause mechanical and physiological pressure changes within a catheter that typically pulls blood into the catheter tip (11, 29). Short peripheral catheters, PICCs and midlines are particularly affected by blood reflux due to their small lumen diameter and high surface area. Complications such as sluggish flow, inability to aspirate blood, loss of patency, fibrin sheath formation, catheter dysfunction and even catheter-related infections are all complications which may be related to blood reflux (30, 31).

NFCs that permit a blood reflux volume  $>10 \mu\text{L}$  allow blood to move beyond the smooth-bore of the distal end of a 20-gauge catheter and into the wider lumen. Any amount of blood moving into the lumen of a catheter may create the opportunity for partial or complete occlusion (13, 32); however, as illustrated in Figure 3, reflux volumes  $>10 \mu\text{L}$  provide greater risk due to the shape of the lumen. While the exact volume of blood reflux into each catheter resulting in occlusion is unknown, greater blood reflux volume and longer time *in situ* will cause coagulation within a catheter lumen. Smaller lumen catheters, such as PICCs and midlines have higher incidence of occlusion and may have greater impact from any amount of blood reflux. Catheter dysfunction with loss of patency is the most common complication of intravascular catheters resulting in significant impact on continued catheter use with added cost associated with treatment or replacement (33-42).

According to Rupp, Jarvis and others, design features and complexities of NFCs create higher or lower risk for vascular access device infection. Vascular access device infection rates have increased in some facilities with the advent of luer-activated mechanical valve NFCs (12, 23, 43, 44). The ability to effectively disinfect the surface area, gaps and hub designs of each connector are listed by Jarvis as characteristics affecting risk of infection (8). Ease of flushing and complete clearance of all blood products and medications within the NFC is another design feature contributing to infection risk. CLABSIs impact patient safety and financial risk. To reduce CLABSIs and complications of occlusion, it is crucial that all blood be adequately flushed from NFCs and the reflux of blood be minimized.

Methods to maintain patency and function of catheters include consistent flushing, standardization of NFCs throughout the facility and frequent education with competency validation on use of NFCs per manufacturer's recommendations. The relationship between blood reflux and occlusion is not clarified in the research, although theoretically NFC pressure control preventing reflux and minimizing blood within the catheter would reduce occlusions while maintaining catheter patency (18, 45, 46). In the Canadian Vascular Access Association (CVAA <http://cvaa.info/PUBLICATIONS/OcclusionMan>

agementGuideline(OMG)/tabid/229/Default.aspx ) Occlusion Management Guidelines, prevention strategies note the need for education to: prevent reflux of blood into the tip of the catheter by avoiding syringe rebound, keeping the infusion rate at a level to avoid pressure changes or stasis, flushing with at least twice the volume of the device and more after blood administration or draws, and consideration for using technology designed to prevent catheter occlusions (39).

For those NFC manufacturers who indicate clamping upon disconnection within the instructions for use, the NFCs are not intended to be used without a clamping sequence. The significance of microliter reflux volumes on each catheter remains speculation; results are currently unknown and are the subject of research to follow this investigation.

### Limitations

While the theoretical/mathematical calculations were useful in identifying best and worst fluid reflux in this in vitro investigation, several limitations prevented the exact prediction of expected reflux with a greater degree of accuracy. The theoretical calculations were based purely on the 3-D model changes in volume and fluid displacement created when the soft silicone septum was compressed by the male luer-lock connector. Additional variables influencing the actual amount of fluid-movement/reflux into the catheter included:

- Amount of pressure or distortion of the soft silicone material within each NFC
- Amount of deflection and speed of contraction of the soft silicone material when engaging luer-lock or cannula to the needle-free IV connector
- The opening and closing of the split septum seals in the soft silicone septum
- The potential for mechanically created fluid movement in and out of the system at different rates due to internal mechanisms, pressures and freely moving bi-directional flow
- Manner in which some irregularly shaped compressible parts fold, and the amounts of residual fluids these parts trap as they fold.

Research performed with theoretic calculations and in vitro testing is a limitation where clinical implications are difficult to define. Clinical relevance of reflux volume in intravascular catheters has yet to be determined. The venous simulation experiments yield insight into the amount of reflux likely to occur with a standard venous pressure of 8 mmHg; however, actual reflux in the clinical setting is influenced by a variety of other factors. Patients are likely to have conditions resulting in abnormal blood pressures (both high and low) (47), abnormal blood viscosity (usually higher) (48) and are likely to experience temporary, often acute, changes in bloodstream pressure due to factors such as bodily movement, coughing, sneezing, etc.

The experimental values of reflux also have their own limitations. First, these values are for unclamped operation. Surprisingly, the clamping sequence in some manufacturer information for use is not specified or not clearly described, whereas others are clear in the instructions for clamping

after disconnection (13, 22, 49, 50). In addition, we have compared the reflux upon disconnection for negative, neutral and anti-reflux connectors to the reflux upon connection for positive connectors. In doing so, we chose to compare the maximum inward movement of fluid into the catheter at any point during the usage of the NFC, which (as highlighted in Tab. I) functionally occurs during connection of a syringe for positive displacement NFCs, and during disconnection for all other NFC types. This difference in functional fluid movement establishes a variable and limitation in direct correlation of results from negative, neutral, anti-reflux and positive displacement NFCs. Surfaces that contact blood (especially surfaces in irregularly shaped regions from which blood may not be completely expelled upon flushing) serve as zones where adverse events such as occlusion formation and bacterial colonization can occur. Thus, our work identifies the way in which NFCs may be expected to perform best, in relation to fluid movement, through both theoretical and actual quantitative measurement methods.

### Conclusion

In conclusion, this study serves as a necessary stepping stone to quantitatively inspect and evaluate commercially available NFCs, while also establishing evidence for education of healthcare providers regarding risk associated with NFCs. These results indicate incorporation of NFC designs with pressure activated anti-reflux diaphragm, which may minimize blood reflux and potentially contribute to the reduction of lumen occlusion. Overall, the results demonstrated significant differences in the volume of fluid reflux based on NFC design. More comparative research on the impact of blood reflux and associated outcomes in intravascular catheters is needed.

### Disclosures

Financial support: This study was funded by a grant to the University of Missouri from Nexus Medical, LLC. Shramik Sengupta PhD, Department of Bioengineering, served as principal investigator on this grant. The funding source played no role in the research results or reporting of the data. The results and conclusions of the research are the work product of the authors. Graphic contributions were received from Nexus Medical.

Conflict of interest: All authors submitted ICMJE Form for Disclosure of Potential Conflicts of Interest. G Hull reported no conflicts of interest, reported no employment and was a full time student. Dr. Sengupta reported serving as a consultant to Fresenius. N Moureau reported employment with PICC Excellence, Inc, Greenville Memorial University and Medical Center, Greenville, South Carolina; educational speaker and consultant to 3M, Angiodynamics, Access Scientific, B Braun, BD Carefusion, Chiesi, Entrotech, Excelsior, Fresenius, Linear Health Sciences, Nexus, Parker Labs, Teleflex, and research grant recipient from 3M, Cook and Entrotech.

This research represents potential limitation and bias due to commercial funding. Experiments and research process was performed independently and exclusively by the University of Missouri research department; the manufacturer had no role in the research results or reporting of the data. The role of the manufacturer was in providing the funding, the product, reviewing the initial objectives and protocol developed by the research department prior to initiation of the study.

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